RECOMBINANT DNA RESEARCH
Volume 4

Documents Relating to "NIH Guidelines for Research Involving Recombinant DNA Molecules" August - December 1978

Appendices

U.S. DEPARTMENT OF HEALTH, EDUCATION; AND WELFARE
Public Health Service National Institutes of Health

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RECOMBINANT DNA RESEARCH

Volume 4

Documents Relating to
"NIH Guidelines for Research
Involving Recombinant DNA Molecules"
August - December 1978

APPENDICES

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Prepared by the
Office of the Director, NIH

DHEW Publication No. (NIH) 79-1876

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

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UNITED STATES DEPARTMENT OF COMMERCE
The Assistant Secretary for Science and Technology
Washington, D.C. 20230
(202) 377-3111

04 AUG 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Don:

Thank you for sending me the three documents concerning the National Institutes of Health (NIH) Proposed Revised Guidelines to control recombinant DNA research funded by the NIH.

As you know, I continue to be deeply interested in the recombinant DNA issue. If we have any observations to make during the period of public comment, beyond those already made at the meetings of the Interagency Committee, I will have Sid Galler pass them to Joe Perpich.

Sincerely,

Francis H. Holek
for Jordan J. Baruch

Columbia University in the City of New York | New York, N.Y. 10027

DEPARTMENT OF BIOLOGICAL SCIENCES

SHERMAN FAIRCHILD CENTER
FOR THE LIFE SCIENCES

August 9, 1978

Donald S. Fredrickson, M.D.
Director
Department of Health, Education
and Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Thank you for sending me the latest on proposed revised guidelines for Recombinant DNA Research (dated Firday, July 28, 1978) in which you asked for my comments in review. This is very easy for me to do since I am opposed to all guidelines (although I will continue to abide by them, of course). My experience in science has convinced me that scientists do a superb job, by and large, of policing themselves. The disastrous effects of discoveries come not from the research laboratory but from the terrible abuses of these discoveries by society. In summary then,I favor the revised guidelines over the previous ones because they represent a relaxation of the restrictions on doing experiments.

Yours sincerely,

Geoffrey Zubay
Professor of Molecular
Biology

GZ/ls

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

CENTER FOR CANCER RESEARCH

77 MASSACHUSETTS AVENUE, CAMBRIDGE, MASSACHUSETTS 02139

August 9, 1978

Dr. Donald Frederickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Don,

I am writing to support issuance of the Revised Guidelines for Recombinant DNA Research as they are described in the Federal Register for 28 July, 1978.

The original Guidelines were purposely designed to be more stringent than most biologists thought necessary because our lack of experience with recombinant DNA seemed to imply a need to err on the side of caution. Revision is now long overdue: we have extensive experience with recombinant DNA and many demonstrations of the power of recombinant DNA methods to advance scientific knowledge. All of the evidence suggests that the original Guidelines were much too restrictive.

I am personally gratified that research will now be speeded in animal virology. With a simplification of containment practices for cloning animal viral DNAs, it will become possible to clone many DNA copies of RNA virus genome and thus, for the first time, it will be possible to derive complete sequence data on such viruses. Progress in all aspects of animal virology will be speeded when the Revised Guidelines are issued with important implications for the improvement of health and well-being in the country and abroad.

I am also gratified to see increased flexibility built into the Guidelines. With research advancing so rapidly, it is difficult to be comprehensive in the Guidelines and therefore opportunity for case-by-case review of new avenues of research is crucial. For instance, use of defective retroviruses as vectors is soon going to be possible but is not covered by the Revision. I trust that when it becomes possible, the RAC will be able to approve use of such

vectors.

One other aspect of the Revision seems most important to me. It is the increased responsibility given to the institutional committees. The flexibility inherent in this shift of responsibility should facilitate research.

Although I fully understand the need to move cautiously in this controversial area of scientific administration, I think that it is time to be firm about what we believe. For too long, the charade of a major bureaucracy overseeing a harmless enterprise has been allowed to continue. While I agree that "a capability must be maintained for observing any capacity of these experiments to yield harmful products" (pg. 33044, from the Director's Decision), I am not happy that "early abandonment" of the Guidelines is not being contemplated. With the present Revision, most of the more complex containment categories will be emptied of relevance and I would very much hope that early abandonment of the Guidelines or replacement with simple, good sense, safe microbiological procedure will be a matter for discussion in the near future. It would be possible to maintain surveillance without interposing a bureaucracy between scientists and their experiments.

Sincerely,

DB/mts David Baltimore

NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS 60201

DEPARTMENT OF BIOCHEMISTRY
AND MOLECULAR BIOLOGY

August 10, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I have carefully read the Proposed Revised Guidelines for recombinant DNA research. I consider the proposed revisions to be a dramatic improvement of the original guidelines. It is especially encouraging to see the recognition of the effectiveness of biological containment. The original guidelines have served their purpose, and are now unnecessarily impeding progress. I urge you to institute the revised guidelines as soon as possible.

Sincerely,

LBDumas

Lawrence B. Dumas
Associate Professor

LBD/jd

MASSACHUSETTS INSTITUTE OF TECHNOLOGY CAMBRIDGE, MASSACHUSETTS 02139
Center for Cancer Research Room E17-529B

August 11, 1978

Dr. Donald S. Fredrickson
Director
Department of Health Education and Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson,

I think revisions of the NIH guidelines are long over due. I fault you and NIH for being so slow and formal in adopting the revisions and hope that after this 105 days of useless waiting, there will be no futher delay. The next and final step in this DNA recombinant guideline farce is to do away with federal guidelines and the expensive paper work involved.

The following comments should be considered in forming the final draft of the guidelines.

1. In Section III-A-2a-(1) DNA Viruses, there should be some stated definition as to whether a DNA virus is a transforming or non-transforming virus. In particular it would be helpful to relate this classification to either class 1-4 of Appendix B or the classification of oncogenic viruses.

2. In Section III-C-1-C-(1), the requirement that defective vectors of Ad5 or 2 have deletions of 2 capsid genes is awkward. The best defective adenovirus vector system available is one where the transforming region of Ad2 or 5 is deleted (making this an absolutely defective virus and a non-pathogen) and the foreign DNA substituted at this site. The growth of the defective virus is complemented by infection of an Ad5 DNA transformed cell line; the 293 cell line. I recommend removing the term capsid and substituting it with essential genes.

3. In Section IV-A-1-d- last sentence of paragraph. I do not believe NIH has a right to require an institution to insure that all principal investigators, irrespective of funding, have agreed to carry out their responsibilities under the guidelines.

Sincerely yours,

Phillip A. Sharp

Phillip A. Sharp
Associate Professor

PAS/ms

THE
UNIVERSITY
OF UTAH

COLLEGE OF MEDICINE
DEPARTMENT OF
MICROBIOLOGY

5C126 MEDICAL CENTER
SALT LAKE CITY, UTAH 84132
801-581-8777

August 12, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Thank you for sending me a copy of the new Proposed Revised Guidlines governing recombinant DNA research and for your invitation to comment on them. I am very much in sympathy with the thinking which has dictated a reduction in most of the containment levels. Both our hazard-free experience over the past 5 years and general considerations of microbial ecology suggest greater confidence that the real dangers connected with recombinant DNA work are minimal. In addition, the very sensible exclusions from jurisdiction of the Guidelines eliminate many absurd restrictions which exist, largely due to oversight, in the current regulations - e.g., the prohibition on cloning Salmonella or Salmonella phage DNA in Salmonella, the use of E. coli strains other than K-12 as hosts of E. coli coliphage recombinant DNAs and the handling of purified DNAs outside host organisms. I am in complete agreement with your request that we should continue to be sensitive to the consequences of the practice of recombinant DNA research. Direct experiments testing potential hazards should also help to determine whether the Guidlines need to be tightened or can be relaxed further.

As you note, flexibility is an important component of the regulation of recombinant DNA research. Retention of final authority for designating containment levels in your office, as opposed to solidifying the designations in federal legislation, seems most sensible. Placement of executive authority for determining compliance with the regulations at the institutional level, particularly with the Institutional Biosafety Committee, represents a major improvement over the present Guidlines. Currently, a great deal of time and effort is lost in abundant correspondence between individual investigators and a distant and sluggish dureaucracy.

The Proposed Revised Guidlines express a welcome reassessment of the safety of recombinant DNA-carrying organisms. I hope we can continue to respond to lessons based on accumulating experience in aiming for efficient and effective levels of regulation or lack thereof.

Yours faithfully,

Dana Carroll

Dana Carroll
Assistant Professor
Department of Microbiology

DC/bjp

NASA

National Aeronautics and
Space Administration

Washington, D.C.
20546

AUG 14 1978

Reply to Attn of: SBL-3(78-375)

Dr. Joseph G. Perpich
Associate Director for
Program Planning and Evaluation
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Perpich:

I have no substantive comments on the proposed revised guidelines. Although the procedures have in some ways been relaxed, I believe they are consistent with the public safety and interest, and that work in the area of recombinant DNA research should proceed accordingly.

Sincerely,

David L. Winter M.D.

David L. Winter, M.D.
NASA Director for Life Sciences

Juvenile Diabetes Foundation

EXECUTIVE OFFICE
23 East 26th Street • New York, New York 10010 • (212) 889 - 7575

August 14th, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Room 124, NIH 1
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

The Juvenile Diabetes Foundation is composed of primarily diabetics and their families. We are not research scientists and, thus, must rely on the advice of distinguished individuals including our own medical science advisory board for their judgment on such issues.

However, we are, I believe informed and intelligent consumers. From this vantage point, I would like to express our opinions regarding DNA research and diabetes.

We are strongly in favor of recombinant DNA research in the area of diabetes. We are also seriously concerned because we believe that there exists a lack of adequate facilities available to pursue this research as fast as it could be pursued given the current scientific knowledge and capabilities.

For the above mentioned reasons, I want you to know that the Juvenile Diabetes Foundation has gone on record time after time after time with Appropriations Committees in the House and the Senate to request additional funding for scientific opportunities in diabetes research. It is our hope that you as the head of NIH will see that an appropriate segment of these monies will be spent on this type of research. In addition, I hope you will let me know so that I can inform our constituentcy (more than 100 chapters and hundreds of thousands of individuals) what further opportunities exists in the area of recombinant DNA research and diabetes that are "approved but unfunded" because of lack of appropriations.

The JDF is a tax exempt, non-profit organization.

As I have mentioned in person during one of our meetings with you, the Juvenile Diabetes Foundation is extremely interested in the availability of insulin that is non-antigenic and which is as close to human insulin as possible. We believe that in the interim, while the scientists are working on a cure for diabetes, non-antigenic insulin would be better for our children that the insulin currently available from animal pancreas. We remain concerned that scientific research in this area is being hampered by restrictions on the ability to pursue recombinant DNA research. I understand from the scientists that the severity of the restrictions has been greatly questioned in the scientific community and we, as the parents of diabetics and as diabetics, implore you to resolve this issue as quickly as possible.

In the meantime, if such restrictions are deemed absolutely and irreconcilably necessary, then we would urge the utilization of resources of the NIH to provide better facilities for DNA research. We intend to pursue a similar position with the relevant member of Congress.

As always, I appreciate your attention to our concerns.

Sincerely,

Carol Lurie

Carol Lurie
President
Juvenile Diabetes Foundation

cc: All Member of the Senate Appropriations Committee
All Member of the House Appropriations Committee
Senator Edward M. Kennedy
Senator Jacob Javits
Senator Richard Schweiker
Congressman Paul G. Rogers
Congressman Tim Lee Carter
Congressman William A. Steiger

UNITED STATES DEPARTMENT OF AGRICULTURE
SCIENCE AND EDUCATION ADMINISTRATION

OFFICE OF THE DIRECTOR
WASHINGTON, D.C. 20250

August 15, 1978

Dr. Donald S. Fredrickson
Director, National Institutes of Health
Department of Health, Education and
Welfare
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Thank you for your letter of July 27 to Dr. Jim Nielson transmitting the NIH Proposed Revised Guidelines for Recombinant DNA Research and the accompanying Decision and Assessment documents. These materials are being reviewed by the USDA Recombinant DNA Committee, together with Drs. Day and Zaitlin, and their comments on sections dealing with the agricultural sciences will be forwarded to you as soon as possible. This interim response pertains to an issue of urgent concern to the agriculture research community.

Details of the issue bothersome to us are covered in a July 27 response from you to Dr. Peter Day giving your decision not to approve the risk/benefit assessment experiments as proposed by Dr. M. D. Chilton and colleagues and conveyed to you by Dr. Day in a letter of May 10, 1978. Whereas your reluctance to approve experiments that are not specifically stated in the 1976 Guidelines is appreciated, some questions arise concerning recent interpretations of the guidelines. I refer specifically to your recent allowance of self-cloning experiments with yeast which appear to involve studies analogous to Dr. Chilton's proposed experiment of reintroducing the shrunken T_i plasmid into Agrobacterium tumefaciens. Moreover, since the ovalbumin DNA is a characterized clone shown to present no biohazard it should be acceptable as a eukaryotic marker in the genetic engineering study described by Dr. Chilton. We feel the precedent for permitting this has been established by the allowance of self-cloning experiments with yeast.

In principle, the risk/benefit assessment experiments described by Dr. Chilton represent the type of studies that must be performed before the feasibility and significance of recombinant DNA in agriculture can be properly and scientifically assessed. USDA feels strongly that the experiments, proposed for our high containment facilities such as Frederick, Maryland, should begin without delay. The extremely restrictive 1976 guidelines have already impeded the application of

recombinant DNA technology to the genetic improvement of food and fiber crops in the United States for 2 years. Awaiting final approval of the new guidelines will only delay us further and may not assure that the experiments can be done then. Therefore, any reconsideration on your part concerning this matter to allow immediate approval will be appreciated.

Sincerely,

ANSON R. BERTRAND
Director
Science and Education

cc:
Peter Day

ROCHE INSTITUTE OF MOLECULAR BIOLOGY

NUTLEY, NEW JERSEY 07110

August 16, 1978

Dr. Donald S. Frederickson, Director
National Institutes of Health
Building 1, Room 124
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Frederickson:

I would like to take this opportunity to comment on the recent revised guidelines for recombinant DNA research. It is obvious that careful thought had gone into this document and the suggested changes make good sense in light of the knowledge that has been gained over the past two years.

As chairman of the Hoffmann-La Roche recombinant DNA biosafety committee, I cannot emphasize how important these guidelines are for those of us in industry who are involved in this area of research. I see no reason why the entire scientific community, academic or industrial, shouldn't endorse this document. Those involved in putting these guidelines together deserve our wholehearted thanks.

Sincerely,

Herbert Weissbach

Herbert Weissbach, Ph.D.
Associate Director

HW:bk

THE UNIVERSITY OF CHICAGO
DEPARTMENT OF BIOPHYSICS AND THEORETICAL BIOLOGY
CUMMINGS LIFE SCIENCE CENTER
920 EAST 58TH STREET
CHICAGO • ILLINOIS 60637

16 August 1978

Dr. Donald S. Fredrickson
Office of the Director
National Institutes of Health
Bethesda, Md. 20014

Dear Dr. Frederickson:

I should like to comment on the proposed revised guidelines for recombinant DNA research published in the Federal Register on July 28, 1978. For the record I should mention that the majority of my publications over the past 20 years have been on viruses that infect plants or bacteria or, more recently, blue-green algae. I was a member of the Virology Study Section in the early 1970's and am its current chairman. My comments follow the contents of the revised guidelines.

I. Scope of Guidelines. This section is a spectacular improvement over the original guidelines. I applaud the language of the statement of purpose and the definition of recombinant DNA molecules. The section on prohibited experiments seems reasonable, except for I-D-3 which prohibits creation of a plant pathogen with increased virulence. There are some experiments involving cloning fragments of the Ti plasmid of *Agrobacterium tumefaciens* that might be interpreted as prohibited under this section but which are, to me, both important and safe. As long as the Director has the power to grant exceptions from this prohibition, and is willing to use that power, I think we can accept the prohibition.

I support wholeheartedly the decision to exempt all "self-cloning" experiments from the guidelines. That should relieve both the institutional committees and the RAC of a mountain of unneeded paperwork.

I also agree with the list of exempted organisms given in Appendix A although I would prefer to see it expanded to include all the organisms on the RAC third list, in appendix D to the Environmental Impact Statement (p. 33158). Furthermore, I would like to see acceptance of the principle that transfer of an R plasmid from an organism to *E. coli* K12 is a sufficient criterion for addition to the exempted list.

II. Containment. This section is also vastly improved. Particularly important is the clarification of the data to be submitted for certification of biological containment level. Of course the procedure will really be improved only if the RAC meets regularly and reviews the submitted data in timely fashion.

III. Containment guidelines for covered experiments. I have read all the new guidelines without encountering a single item to complain about. It is particularly important to me that the experiments of section III-A-1-b(2) remain no higher than P2+EK1, that the recombinant DNA be returnable by transformation to the cell of origin of the cloned insert, and that the IBC be empowered to lower containment when the cloned material contains no harmful genes. I was also glad to see, in section III-C-2, that the silly business about using insect viruses as vectors for other DNA segments was removed. The section as written is now appropriate.

IV. Roles and responsibilities. I am in agreement with all of the changes proposed in this section as well. The expanded role of the IBC is a particularly important feature. While some critics may see this change as a step toward "deregulation," in fact it merely recognized a de facto situation: only the local committee can possibly judge whether an investigator is competent and his containment adequate. National or state commissions with teams of inspectors would be ineffective and extraordinarily expensive.

Permitting experiments to begin once they are approved by the IBC is an extremely important positive change. That will streamline the procedures immensely and remove delays that have unnecessarily held up good experiments in the past.

I did not notice a procedure for appealing a decision of the local IBC against a project or against certification of a facility.

Membership in the RAC should not include persons selected for their known views, either as cloners or dissenters from the majority. I should hope that committee members are chosen on the basis of their knowledge, integrity, and genuine concern for both safety and the traditional freedom of inquiry on which the scientific power of the United States is based.

In summary, I am strongly in favor of the proposed revised guidelines. They provide adequate protection for the public and interfere much less with scientific progress than the 1976 version. I hope they make legislation affecting recombinant DNA research totally unnecessary.

Sincerely yours,

Robert Haselkorn

Robert Haselkorn

F.L. Pritzker Professor and Chairman

RH/bpm

ROCHE INSTITUTE OF MOLECULAR BIOLOGY

NUTLEY, NEW JERSEY 07110

August 16, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20016

Dear Dr. Fredrickson:

I have received a copy of the Proposed Revised Guidelines for Recombinant DNA Research (Federal Register 43, 33042-33178). While I am in agreement with almost all the RAC proposed revisions and their reasons for them, I would like to question the following:

The proposed containment for shotgun recombinant DNA work on non-primate mammals and birds is P2 + EK2, yet for cold-blooded animals, plants and many of the RNA and DNA viruses it is P2 + EK2 or P3 + EK1. Is there a sound scientific basis for not also allowing non-primate and bird recombinant DNA work to be also carried out under P3 + EK1? The restriction to the use of only P2 + EK2 is not a trivial point, since many experiments using EK1 vectors are extremely difficult, indeed some simply impossible (e.g., those involving lysogenic λ systems) in an EK2 system. In particular, I find it difficult to see why segments of some transforming viruses may be cloned under P3 + EK1 conditions, yet DNA from a non-primate mammal or bird in which any one sequence is diluted out at least one in 10^5 with the other sequences present cannot be carried out under these same conditions.

I would appreciate it if you could bring to the attention of the Advisory Committee this suggestion, i.e., allowing non-primate and bird shotgun DNA experiments at P2 + EK3 or P3 + EK1 levels.

Yours sincerely,

John Monahan

John Monahan, Ph.D.
Department of Cell Biology

JM:SK

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

CENTER FOR CANCER RESEARCH

77 MASSACHUSETTS AVENUE, CAMBRIDGE, MASSACHUSETTS 02139

Room E17-539 Tel. 617/253-3015

August 16, 1978

Dr. Donald Frederickson
Director, NIH
Building 1 - Room 124
9000 Rockville Pike
Bethesda, MD 20014

Dear Dr. Frederickson:

This letter responds to the request for comments on the proposed revised guidelines for recombinant DNA research issued July 28.

The guidelines appear reasonable in light of present knowledge and the relaxations in particular fully merited by the data available. Requiring no mouth pipeting at the P-1 level enforces good laboratory practice for protection of workers (largely from discomfiture).

I hope that as experience grows and - as I expect - the safety of this research is even better demonstrated that we will see continued cutting of the red tape developed for recombinant DNA research and either dismantling of the bureaucracy developed to cope with it or redirecting of it towards biohazards of greater potential.

Sincerely,

Michael D. Garrick

Michael D. Garrick
Assoc. Prof. Biochem. and
Res. Assoc. Prof. Pediatrics
SUNY Buffalo
On study leave

MDG/srp

ENVIRO CONTROL, INC.

One Central Plaza
11300 Rockville Pike
Rockville, Maryland 20852
Telephone: 301-468-2500

August 17, 1978

Dr. Donald S. Fredrickson
Director, National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

The purpose of this letter is to provide comment on certain elements of the Proposed Revised Guidelines for Recombinant DNA Research published in Part IV of the Federal Register for Friday, July 28, 1978.

The comments offered are:

1. It is suggested that the terminology "working area" (Ref. para. II-B-1-a-(5)) and "laboratory area" (Ref. paras. II-B-2-a-(5) and II-B-3-a-(5)) be clarified. The use of the two different terms in describing the prohibited locations and the word area are felt to be unclear and thus subject to varying interpretations.

   It is suggested that the cited paragraphs be changed to read, "Eating, drinking, smoking, or the storage of food are not permitted in the laboratory(s) or other rooms in the facility in which recombinant DNA materials are handled."

   The suggested revised wording is offered since it extends the prohibition to all spaces in a facility in which recombinant DNA materials may be handled, e.g., instrument rooms, glassware, refrigeration equipment rooms, etc.

2. It is suggested that the second sentence of paragraphs II-B-2-a-(11) and II-B-3-a-(11) be amended to read - Freezers, refrigerators, <u>or other units</u> used to store. . ..

   The insertion of the words "other units" provides for including all possible storage units while using the words freezer and refrigerator to typify such units.

It is to be noted that the requirement to post the universal biohazard sign on freezers and refrigerators has been omitted from paragraph II-B-4-a-(15), although paragraph II-B-4-a-(8) does provide for the removal of viable or intact biological materials from a P4 facility. It is suggested the requirement for identifying storage units be included in paragraph II-B-4-a-(15).

3. It is suggested that the reference to Horsfall units in paragraph II-B-3-b-(2) be cited in the bibliography. The appropriate citation is: Horsfall, F. L., Jr. and J. H. Baner (1940) Individual Isolation Of Infected Animals In A Single Room. J. Bact. 40, 569-580.

4. In paragraph II-B-3-c-(7)(line 8), it is suggested that the word recirculation be replaced with the word reconditioning.

   This suggestion is made since it is apparently the intent of this provision to permit the installation of conditioning units in rooms having large heat loads in order to reduce the ventilation requirements. Thus, the word reconditioning would reflect the intent to permit treatment of the air relative to temperature control rather than the movement of air as is indicated by the word recirculation.

   It is also suggested that paragraph 3, under P3 Level (pp. 3314), Proposed Action; Environmental Impact Assessment be amended to reflect the reconditioning of air.

5. It is suggested that the word sterilized be used in lieu of the word decontaminated in paragraphs II-B-1-a-(3), II-B-2-a-(3), II-B-3-a-(3), and II-B-4-a-(3).

   The suggestion to use the word sterilized is based on the precision offered in relation to the destruction of viable organism in contrast to decontamination which refers to the removal of a contaminant. The word sterilized also serves to identify processes or methods for effecting the destruction of viable organisms.

The foregoing are offered as constructive comment and in the interest of contributing to the conduct of research with recombinant DNA molecules. You and your staff are to be complimented for having developed a comprehensive and rational set of guidelines.

Sincerely,

Robert W. McKinney, Ph.D.

RWMcK:kgr

ALBERT EINSTEIN COLLEGE OF MEDICINE
OF YESHIVA UNIVERSITY

1300 MORRIS PARK AVENUE, BRONX, N.Y. 10461 • CABLE:EINCOLLMED, N.Y.

DEPARTMENT OF MOLECULAR BIOLOGY

PHONE: (212) 430-2000

August 18, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Washington, D.C.

Re: Inclusion in the revised guidelines of Caulobacter as an organism which naturally exchanges chromosomal genes with E. coli

Dear Dr. Fredrickson:

I have just received a copy of Bert Ely's manuscript which he has submitted to Genetics for publication. This manuscript amply demonstrates the transfer of chromosomal genes between E. coli and Caulobacter. It is, therefore, quite appropriate that Caulobacter be included on the list of exchangers in Appendix A of the proposed revision of the NIH Guidelines for Recombinant DNA Research. Such an inclusion would greatly facilitate experiments in progress in my own laboratory on the organization and expression of the Caulobacter genome during the course of cell differentiation. Similar studies are concurrently progressing in several other laboratories studying Caulobacter.

The overall revision of the guidelines will permit work in the areas of microbial gene expression to proceed at a faster rate and in general to be more productive. I feel the Recombinant DNA Committee has done an excellent job in revising the guidelines, and that the revisions are both realistic and logical.

Sincerely yours,

Lucille Shapiro

Lucille Shapiro
Siegfried Ullmann
Professor of Molecular Biology and
Chairman of the Department

LS/ac

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

TO : Director, NIH

DATE: August 18, 1978

FROM : Chief, Laboratory of Biochemistry DCBD, NCI

SUBJECT: Proposed Revised Guidelines for Recombinant DNA Research

1. I have read the Proposed Revised Guidelines for Recombinant DNA Research carefully and with great interest. I believe that a remarkably good job has been done in the revision process and that if approved, the new Guidelines will be far superior to the old ones.

2. I would like to disagree with the second paragraph of Section III-A-1-a, which addresses the question of whether one should be allowed to replace P2+EK2 with P3+EK1. Such replacement has been specifically interdicted in the case of DNA from birds. I believe that such replacement should be allowed in the case of avian DNA. I am currently engaged in recombinant DNA experiments utilizing shotgun techniques for inserting chicken DNA fragments into bacterial phages and plasmids, utilizing EK2 host-vector systems and the P3 level of containment. The birds we work with are highly inbred, are maintained on feed that is free of antibiotics, nitrofurans, arsenicals, and all pesticides currently assayed by the FDA, and have been shown by the appropriate testing procedures to be free from Pollorum typhoid, Mycoplasma gallisepticum, Mycoplasma snyoziae, Salmonella typhimurium, and avian leukosis virus. I do not see any reason for requiring an EK2 system for our experiments carried out in a P3 facility

3. Another suggestion I would like to make concerns the details of the P3 level of containment. I believe that it would be wise to require that booties must be worn at all times within the P3 lab, just as gowns must be worn. It seems to me that the force of gravity tends to make the floor the most likely place for any contaminating substance to end up, not only in the case of an accidental spill of gross proportions. Since shoes are an ideal mechanism for carrying material into and out of rooms, I think they should be covered. I have, in fact, instituted an absolute rule that booties must be worn in my P3 facility and I suggest that this procedure be made part of the guidelines requirements.

4. As a scientist with a deep concern for the need to protect the experimentalist and the public at large from the potential hazards of scientific research, I applaud the revised guidelines as a document that will provide excellent protections while not severely impeding research. Because of the safeguards built into the guidelines and because of the heightened awareness of the scientists engaged in recombinant DNA research, I now consider my P3 facility to be the safest room in Building 37, both for those who work inside it and for those who do not.

Robert Goldberger, MD

Robert Goldberger, M.D.

ROCHE INSTITUTE OF MOLECULAR BIOLOGY

NUTLEY, NEW JERSEY 07110

August 18, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Building 1, Room 124
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

The "Proposed Revised Guidelines for Recombinant DNA Research" represent a major improvement over the present guidelines. I strongly support the revised guidelines.

I would like to point out an apparent inconsistency in the revised guidelines which permit tumor viruses to be used with more flexibility and under less stringent conditions than other eukaryotic tissues. For example, shotgun experiments with primate DNA or cDNA require P2-EK2 conditions whereas clones containing genomic segments of transforming viruses can be manipulated under P2-EK2 or P3-EK1 conditions. It seems that primate DNA or cDNA should be able to be handled under conditions permitted for primate transforming viruses. Therefore, I recommend that the final version of the new guidelines permit shotgun experiments with eukaryotic DNA [Section III-A-1-a] under P2-EK2 or P3-EK1 conditions. This would include shotgun experiments with DNA or cDNA from primates, other mammals and birds as detailed in Sections III-A-a-(1), III-A-1-a-(2), and III-A-1-a-(3), respectively.

I hope that this change shall be incorporated in the new guidelines.

Sincerely yours,

Sidney Pestka

Sidney Pestka
Adjunct Professor of Pathology
College of Physicians & Surgeons
Columbia University

SP:mi
cc: Dr. H. Weissbach
Dr. William J. Gartland, NIH
Dr. Daphne Kamely, NIH

NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS 60201

DEPARTMENT OF BIOCHEMISTRY
AND MOLECULAR BIOLOGY

18 August 1978

Donald S. Fredrickson, Director
National Institutes of Health
Bldg. 1, Room 124
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I read the proposed revisions of the guidelines governing NIH-sponsored recombinant DNA research with great interest. First, let me say that I strongly endorse the general relaxation of the current guidelines. I agree with the report (p. 33047, Federal Register, Vol. 43, No. 146) that in view of the recent findings in both viruses and eucaryotic structural genes (i.e., that intervening sequences interrupt coding portions of genes), the possibility of genes of higher organisms being expressed in procaryotic hosts is greatly reduced. It appears that nature has already provided a more stringent requirement for expression than we had perceived, and also probably provides better safety features than those presently used in our EK2 host/vector constructs. (I feel compelled to point out that this change in our perception was obviously the result of structural studies on recombinant DNA's by Leder and Chambon, and the use of recombinant DNA probes by Flavell).

Thus, I think that the decision to revise the guidelines to allow research under more relaxed physical and/or biological containment conditions is both judicious and timely.

Sincerely,

Doug Engel

James Douglas Engel, Ph.D.
Assistant Professor

JDE/kaf

VSSR

VAN WERT • SNYDER • SKLARSKY • ROWLEY
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Department of Health, Education and Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Attn: Dr. Donald F. Fredrickson, Director

Gentlemen:

Appreciate receipt of July 28th Federal Register covering Proposed Revised Guidelines for Recombinant DNA Research. Our firm is deeply involved with the use of these guidelines in preparing working drawings for the National Biomedical Containment Laboratory at Frederick Cancer Research Center and I consider it an honor to accept your invitation to submit comments on the proposed revisions.

In addition to the suggestions contained herein, I have also enclosed a tabulation of the physical containment portion of the guidelines covering Laboratory Practice, Containment Equipment and Special Laboratory Design. This document was prepared by our office to assist our staff in comprehending and comparing the various requirements at a glance. Needless to say, it has proven most valuable not only in our design work on the above project, but also on the Cancer Research Containment Facility recently prepared for Roswell Park. I submit it to you hoping you may find it useful as a handy reference.

Comments on the Proposed Revised Guidelines are referenced to Federal Register page numbers as follows:

1. Page 33074, Section II-B-4-a-(14)

   In listing the required laboratory clothing included, I noted that gloves have been deleted. It would seem that the use of gloves would be utmost impartant in P-4 work since they are required in P-3 labs.

   Later in this same paragraph, it refers to "discarding contaminated clothes into collecting hampers" but does not indicate that these clothes should be decontaminated before being sent to the laundry.

Formerly "Office of J. Fruchtbaum Associates"

VSSR

2. Page 33075, Section II-B-4-c-(12) states "The exhaust air from the P-4 facility shall be filtered and discharged to the outdoors". I noted that the abbreviation HEPA had been omitted before the word "filtered". This may have been done inadvertently, but certainly should be reinstated since without HEPA filters there is no reason for certification testing as referred to at the end of this paragraph.

3. Page 33075, Section II-B-4-c-(14), the reference to "The exhaust air from the suit area shall be filtered by two sets of HEPA filters installed in series and a duplicate filtration unit and exhaust fan shall be provided." probably has been highly contested. Logically, if a substance passes the first filter it will also pass the second in the series since both filters are of the same arresting capacity. However, should the one filter rupture due to unforseen circumstances, the other filter would still maintain the integrity of the system. The duplicate filtration system could also be arranged to automatically be put into service should the primary filters or fan fail, thereby maintaining the constant negative pressure so necessary for the suit area.

   In this same section, the second paragraph states, "The internal shell of the suit area shall be airtight." This should be qualified either by making it comparable to the language used on previous page, Section II-B-4-c-(12) or stating the permissible leakage rate similar to that used in the table concerning the tightness of Biological Safety Cabinets. The specific gas to be used for testing the tightness should be so stated not only in this case, but also for the Biological Safety Cabinets.

I trust the above will be considered of some value in finalizing the revision to the guidelines. I have not offered comments on the biological aspects of containment because this is beyond the scope of my ability as an engineer.

Sincerely yours,

John P. Hutten

John P. Hutten, Project Engineer

JPH:sh

Department of Energy
Washington, D.C. 20545

AUG 21 1978

Dr. Joseph G. Perpich
Associate Director for
Program Planning and Evaluation
Department of Health, Education, and Welfare
National Institutes of Health (NIH)
Bethesda, Maryland 20014

Dear Dr. Perpich:

As requested in your letter of August 7, 1978, documents supporting the Proposed Revised Guidelines to control recombinant DNA research funded by the NIH have been reviewed and the following comments are submitted.

1. No specific changes are proposed to the Revised Guidelines as published in the Federal Register (Part IV) on Friday, July 28.

2. I believe the Guidelines to be fully adequate to protect the public and the environment from any hazards associated with recombinant DNA research.

3. I concur in the conclusion of the Environmental Impact Statement (EIS) that "there would be no adverse impact upon the environment of the NIH-proposed changes in the Guidelines."

Thank you for the opportunity of reviewing the Proposed Revised Guidelines.

Sincerely,

W. H. Weyzen

Walter H. Weyzen, Manager
Human Health Studies Programs
Division of Biomedical and
Environmental Research

UNIVERSITY OF VIRGINIA
SCHOOL OF MEDICINE - BOX 441
CHARLOTTESVILLE, VIRGINIA 22901

DEPARTMENT OF MICROBIOLOGY

August 21, 1978

Donald S. Frederickson, M.D.
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Frederickson:

I am writing to offer my wholehearted support of the Proposed Revised Guidelines for Recombinant DNA Research as reported in the Federal Register of Friday, July 28, 1978 (Part IV).

After reading the documents carefully, I can endorse, without any reservations, all the proposed guidelines proposed by the Recombinant DNA Advisory Committee. I also believe you were wise to retain and expand the restriction on mouth pipetting for all recombinant DNA research and to warn against the prospect of lifting all restrictions in the future. My colleagues and I have no objections to any of the well-considered guidelines and their supervision by local committees with public representation.

You and Secretary Califano are to be congratulated on your excellent statements and the exceedingly well balanced manner in which you have handled this whole thorny affair. You certainly have the support of the overwhelming majority of the scientific community and, I am sure, of most of the public at large. Great strides can now be made under reasonable conditions affording virtually absolute safety. I would only strongly urge the Secretary to delegate to you and your Advisory Committee the authority to continue your review of the guidelines in the future in order to be able to revise them as required when new data become available.

I trust that the revised guidelines can be implemented without delay following the public hearing in September.

Sincerely yours,

Robert R. Wagner

Robert R. Wagner, M.D.
Professor and Chairman

RRW:lrp

COPEWOOD STREET/CAMDEN, NEW JERSEY 08103/(609) 966-7377 (215) MA 7-4855/CABLE ADDRESS: INMEDRES

INSTITUTE FOR MEDICAL RESEARCH

"NON-PROFIT"

August 21, 1978

Donald S. Frederickson, M.D.
Director
National Institutes of Health
Room 124, Building 1
Bethesda, Maryland 20014

Dear Dr. Frederickson:

Re: Recombinant DNA Research
Proposed Revised Guidelines

I have reviewed the revised guidelines and strongly endorse changes which make the guidelines less restrictive. It is obvious that fears of possible harmful effects raised by some scientists were unwarranted and have not been confirmed by experience. Sensational speculative journalistic comment has been recognized as such by the public and by leaders in Congress. The dangers are minimal.

On the other hand, the benefits are real, are being achieved, and have great potential for better understanding the chemistry of living cells in health and disease. I think time will show the recombinant DNA technique to be the major biological scientific achievment of our generation. The proposed revised guidelines are in accord with this evaluation and may be relaxed further if and as warranted by further study.

On the matter of legislation, I see no need for Congress to act at this time. Control can be exercised through Section 361 of the Public Health Service Act. The contents of a letter dated June 1, 1978 from Senators Kennedy, Javits, Nelson, Stevenson, Williams and Schweiker to Joseph Califano set forth the Senate position that regulation can best be handled without additional legislation. Their position is in accord with all the facts that have been developed since the guidelines were first drawn up.

An effort should be made to explain the process to the public in terms they can understand when the new guidelines are issued. My effort to do this for the local press is enclosed.

Sincerely yours,

Lew Coriell

Lewis L. Coriell, M.D., Ph.D.
Director

LLC:dmm
Enclosure

DIRECTOR: LEWIS L. CORIELL, M.D., PH.D

BOARD OF TRUSTEES: WILLIAM H. BELL, JR. • STANLEY S. BERGEN, JR., M.D. • KARL H. BEYER, JR., M.D., • MARVIN COHEN • LEWIS L. CORIELL, M.D., PH.D. • JEAN CORTNER, M.D. • RAE CROWTHER • W. ROBERT DAVIS • JOHN T. DORRANCE, JR • ALEXANDER FEINBERG, ESQ. • MRS. W. H. K. FLECK • MRS. VIRGINIA GRAHAM • FREDERICK P. GREINER, ESQ. • MICHAEL J. HAYES • WILLIAM KALELLIS • FRANK K. KELEMEN • KENNETH N. MACDONALD • GAY A. MAYER • JOHN F. MEADE, JR. • MRS. ALBERT B. MELNIK • WILLIAM R. MORRIS • WARREN W. NICHOLS, M.D., PH.D. • WILLIAM G. O'BRIEN • W. T. READ, M.D. • JONATHAN E. RHOADS, M.D. • A. WEIR STEDMAN • F. WILLIAM STORCK • NEIL VANDER OUSSEN

UNIVERSITY OF SOUTH CAROLINA

COLUMBIA, S. C. 29208

DEPARTMENT OF BIOLOGY

August 21, 1978

Dr. Donald S. Fredrickson
Director
National Institute of Health
Bethesda, Md. 20014

Dear Dr. Fredrickson:

I am writing you concerning the proposed revision of the NIH Guidelines for Recombinant DNA Research. First let me say that I am very much in favor of the revision. I think that the original estimation of the potential biological hazards was overstated and unrealistic. Clearly many dangerous pathogens can be studied more safely after they have been dismantled using "recombinant DNA techniques". Also, the exemption from the Guidelines of bacteria which exchange genetic material with E. coli will eliminate a lot of red tape without any additional risk.

With regard to this last point, I would like to request that Caulobacter crescentus be included in the list of exchangers that is exempt from the Guidelines. I have previously shown that E. coli and C. crescentus exchange plasmids (Abs. Ann. Meeting Amer. Soc. for Microbiol. 1978:109). Additional data is in the enclosed manuscript which I have submitted for publication in GENETICS. In this manuscript, I present data demonstrating exchange of chromosomal genes between E. coli andl Caulobacter crescentus (p.9). This exchange proceeds in either direction and is dependent upon the presence of a drug resistance factor in the donor. I feel that these data are quite sufficient to meet the criteria for exchanges as described in section I-E-4 of the Guidelines and that Caulobacter crescentus should be included in the list of exchangers in Appendix A of the proposed Revision. Thank you in advance for your help on this matter.

Sincerely,

Bert Ely

Bert Ely
Assistant Professor

BE:kf

The University of South Carolina: USC Aiken; USC Salkehatchie, Allendale; USC Beaufort; USC Columbia; Coastal Carolina College, Conway; USC Lancaster; USC Spartanburg; USC Sumter; USC Union; and the Military Campus.

DEPARTMENT OF AGRICULTURE
OFFICE OF THE SECRETARY
WASHINGTON, D. C. 20250

AUG 22 1978

Donald S. Fredrickson, M.D.
Director, National Institutes of Health
Department of Health, Education, and Welfare
Bethesda, Maryland 20014

Dear Dr. Fredrickson: Don

Thank you for your letter of August 3 and the three documents published by NIH for public comment: (1) Decision of the Director, (2) Proposed Revised Guidelines--NIH, and (3) Environmental Impact Assessment.

I was pleased the report of the Risk Assessment Workshop of Agricultural Pathogens was included and that it has been incorporated into the proposed revised guidelines. Specific comments on Section III of the guidelines will be forwarded to you in early September.

The revised guidelines would permit certain recombinant DNA experiments that have the potential for enhancing food and fiber production significantly. We are, therefore, supportive of their early approval.

Sincerely,

Rupe

M. RUPERT CUTLER
Assistant Secretary for
Conservation, Research, & Education

I'll push to get our comments out as quickly as possible

jl

Scripps Clinic and Research Foundation

10666 North Torrey Pines Road
La Jolla, California 92037 (714) 455-9100

August 22, 1978

Donald S. Fredrickson, M.D.
Director
National Institutes of Health
Bethesda, Maryland 20014

RE: Recombinant DNA Research
Proposed Revised Guidelines

Dear Dr. Fredrickson:

Since the beginning of the recombinant DNA affair, I have never seen evidence to substantiate the view that any organism containing any artificially produced recombinant DNA molecule is more pathogenic than the donor from which it was formed. No such evidence is known to science. Therefore, no regulations are needed whatsoever, because none have been required with known pathogens.

I suggest the whole set of guidelines be replaced by the following sentence:

> "It would seem prudent to conduct work with organisms containing recombinant DNA under laboratory conditions appropriate to the degree of pathogenicity of the donor organisms."

We find ourselves in a horrible mess created by a few scientists who have behaved in a totally unscientific and irresponsible manner under the banner of "responsibility." This unscientific activity has been going on for some time, as I try to show in the enclosed article.

Yours sincerely,

Charles A. Thomas

Charles A. Thomas, Jr.
Chairman, Department of
Cellular Biology

CAT:dw
enc.

"Fanciful Future of
Gene Transfer Experiments"
Brookhaven Symposia, No. 29, 1977

ST. JUDE CHILDREN'S RESEARCH HOSPITAL

332 North Lauderdale, P.O. Box 318,
Memphis, Tennessee 38101
(901) 525-8381

Danny Thomas, Founder

23 August 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

As a working virologist for nearly thirty years, I am writing in support of the revised safety guidelines for recombinant DNA research published in the Federal Register of 28 July 1978. The final guidelines should be issued without delay and implemented promptly if Congress does not pass a bill dealing with recombinant DNA research.

I believe there is more than sufficient information available now that warrants liberalization of the 1976 safety guidelines. Depending on the course of events by upper echelons of government, I hope you will implement the revised guidelines at the earliest time so as to move forward this extremely important area of biomedical research.

Sincerely,

Allan Granoff

Allan Granoff, Ph.D.
Chairman, Division of Virology
St. Jude Children's Research Hospital
Professor of Microbiology
University of Tennessee Center for the Health Sciences

AG/jh

THE UNIVERSITY OF CHICAGO
DEPARTMENT OF BIOPHYSICS AND THEORETICAL BIOLOGY
CUMMINGS LIFE SCIENCE CENTER
920 EAST 58TH STREET
CHICAGO • ILLINOIS 60637

23 August 1978

Dr. D. Frederickson
Office of the Director
National Institutes of Health
Bethesda, Md. 20014

Dear Dr. Frederickson:

After reading the revised guidelines for Recombinant DNA research I find them extremely appropriate. They provide the necessary safeguards to conduct reconbinant DNA research with the possibility of performing experiments which eventually will yield further advancements in all areas of biological research.

Sincerely yours,

Lucia B. Rothman-Denes
Assistant Professor

LBRD/bpm

THE UNIVERSITY OF CHICAGO
DEPARTMENT OF BIOPHYSICS AND THEORETICAL BIOLOGY
CUMMINGS LIFE SCIENCE CENTER
920 EAST 58TH STREET
CHICAGO • ILLINOIS 60637

August 23, 1978

Dr. Donald S. Fredrickson
Office of the Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I have read the revised NIH guidelines for recombinant DNA research and support their adoption. I am especially pleased that more responsibility has been delegated to the institutional biohazard committees, thereby eliminating some of the delays associated with recombinant DNA experiments. I am also pleased that self-cloning will be permitted, and that recombinant DNA can be returned to the organism from which it was derived. Although the new containment level for prokaryotes not exchanging DNA with E.coli, P2-EK1, is an improvement over the old designation, I feel that it is still overly restrictive. I do not understand why recombinant DNA experiments involving the cyanobacteria Anabaena require P2 facilities, and feel these experiments should be classified P1-EK1. With the exception of this minor reservation, however, I wholeheartedly support the adoption of the revised guidelines.

Sincerely yours,

Barbara Mazur

Barbara Mazur

BM:dw

THE UNIVERSITY OF CHICAGO
COMMITTEE ON GENETICS
920 EAST 58TH STREET
CHICAGO · ILLINOIS 60637

August 24, 1978

Dr. Donald S. Frederickson
Director, National Institutes of Health
Building 1, Room 124
Bethesda, Maryland 20014

Dear Dr. Frederickson:

I write to express my approval of the new Guidelines for Recombinant DNA Research recently published in the Federal Register. These revised guidelines strike a reasonable and realistic balance between risks and benefits. We do not know what dangers, if any, can be expected from new recombinant DNA experiments. The restrictions will provide adequate safeguards to prevent harm. On the other hand, the proposed guidelines allow a reasonable reduction in the restrictions so that work of great scientific interest and potential benefit can proceed expeditiously. I urge that these revised guidelines be adopted.

Sincerely,

Wolfgang Epstein

Wolfgang Epstein
Chairman

WE/gb

ST. JUDE CHILDREN'S RESEARCH HOSPITAL
332 North Lauderdale, P.O. Box 318,
Memphis, Tennessee 38101
(901) 525-8381
Danny Thomas, Founder

24 August 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Building 1, Room 124
9000 Rockville Pike
Bethesda, MD 20014

Dear Dr. Fredrickson:

I am writing as a practicing molecular biologist to urge the adoption of the Proposed Revised Guidelines for recombinant DNA research funded by the National Institutes of Health, as published in the Federal Register of 28 July, 1978.

According to past and recent experience, potential hazards of this research were imaginatively overestimated by some individuals. There now seems to be no justification for continuing to enforce restrictions that are scientifically unsupported and which are interfering with the performance of work for the benefit of society.

Sincerely,

David W. Kingsbury

David W. Kingsbury

DWK/jh

STATE OF CALIFORNIA — HEALTH AND WELFARE AGENCY

EDMUND G. BROWN JR., Governo

DEPARTMENT OF HEALTH SERVICES
714/744 P STREET
SACRAMENTO, CA 95814
(916) 445-8706

August 24, 1978

Dr. Donald S. Fredrickson, Director
National Institute of Health
9000 Rockville Pike
Bethesda, MD 20014

Dear Dr. Fredrickson:

Thank you for inviting comment from members of the public on the newly revised NIH Guidelines for Recombinant DNA Research, as they appeared in the July 28, 1978 Federal Register.

I am writing in my capacity as a public health official, but my views do not necessarily reflect those of the California Department of Health Services which is preparing a formal response from the Department to be sent under separate cover.

My response bridges three areas: Administrative, Procedural and Substantive. In general, I find the document reflects a thoroughness in scientific review of research objectives which might be safely met which is not found in the treatment of the public health implications of the same work.

1. Administrative Concerns

A. I would like to have seen a greater involvement of OSHA and EPA in the review of the research protocols in relevant classes of research, i.e., those which pose potential occupational hazards or environmental problems on the basis of research design and strategy. For instance, the proposed Guidelines only specify that the requirements of the National Environmental Policy Act be "considered" as a precondition for a waiver for environmental release of recombinant organisms.

1) Recommendation

I would like to see much stronger language requiring compliance with NEPA, with the notation that any additional safeguards to be stipulated by EPA are to be honored.

B. I find the present document seriously remiss in not acknowledging the priority of local health departments in determining whether or not

health risks are attendant to any non-compliance, particularly that which results in a "spill" or otherwise exposes the population to potentially harmful recombinant organisms. Presently, the Guidelines simply require a report to the local Biosafety Committee and NIH. [Sec. IV-A-4-h]

1) Recommendation

Require that any research which is found to be out of compliance with NIH be reported to the State Department of Health or its local equivalent; and that any release of recombinant organisms, regardless of suspected pathogenicity, be reported to the proper health authorities.

While I recognize the difficulty of a federal body mandating local activities, the fact that the research in question will be under federal aegis, means that the Federal Government must accept responsibility for any untoward health consequences. At a minimum, this requirement would reduce the imperative felt by many states to establish their own conditions for regulating recombinant DNA research.

2. Procedural Concerns

A. As presently drafted, the Guidelines lack specificity in establishing the conditions for minimizing risks once an accident has occurred.

1) Recommendation

Include specifications for cleanup procedures to be followed should there be a spill or accidental release of organisms into the environment. Such procedural safeguards should incorporate the suspected pathogenicity or hazard posed by the released organism.

B. The Guidelines do not establish a central clearing house which would record and monitor the nature and kind of organisms being used in recombinant DNA work and collect data regarding the safety record of particular laboratories.

1) Recommendation

Identify an appropriate agency within NIH to maintain such data, including accurate records of workers in recombinant DNA work, with particular regard to the incidence and severity of possible work related illness; or, require that special reporting requirements be met by research laboratories with their respective Biosafety Committees, who in turn will file reports with State or local agencies.

C. While the new proposed guidelines acknowledge the problem of certification (p. 33132) and considerable more input from laboratory health experts, e.g., on your decision regarding mouth pipetting, they still do not require the special training procedures which are now standard for certain laboratories doing work with pathogenic organisms.

1) Recommendation

Specify that lab workers in P2 and higher facilities take and pass certain training courses, or demonstrate equivalent competency, prior to working directly with recombinant DNA organisms. A centralized and uniform certification process would be extremely desirable for P3 and P4 level workers.

D. The policy on noncompliance is vague and weak. It invites too much latitude in defining penalties by encouraging discretion to be used, from exoneration to full penalties, without mention of due process to injured parties (i.e., workers).

1) Recommendation

Sec. IV-D-1-b on Page 33087, remove the word "may" and replace with "shall ... upon an affirmative finding after due process, that a willful violation has in fact occurred. Negligence may result in similar suspension, limitation, or termination of NIH funds."

3. Substantive Concerns

A. The premise on which containment levels for shotgun experiments was lowered is problematic. If in fact eukaryote DNA contains intragenic DNA, such that maturation mechanisms are necessary to effect gene expression, it does not follow that all such eukaryote genes have such molecular spacers: certainly, this would be unlikely for short but biologically active polypeptides like bradykinin where only 7, 8 or 9 amino acids are necessary for biological activity. Moreover, since it is possible if not likely (as many recombinant DNA proponents argue) that genic exchange has been going on across phylogenetic barrers, why would it not be likely that eukaryotic DNA includes segments of potentially active DNA from procaryotes.

1) Recommendation

Potentially recombinant DNA shotgunned from such organisms, e.g., birds and mammals other than primates, should either be tested for such sequences (perhaps by hybridization studies with the DNA of their natural commensals and intestianal flora); or the necessary experiments left at the P3 and EK2 level.

B. The present Prohibitions (Sec I-D) are insufficiently precise. For instance on page 33070, Sec I-D-3, the use of the phrase "beyond that which occurs by natural genetic exchange" allows a researcher to produce any pathogen duplicated by natural recombination, even if that agent has been eliminated through selection. Similarly, Section I-D-5 permits the same "natural" test to apply to the acquisition of drug resistance. Thus, the fact that a rare strain of Francisella pestis or Tularemia species has on occasion been found with antibiotic resistance genes acquired by R factor transfer would sanction the intentional introduction of similar genes by artificial means.

The additional stipulation in I-D-5 which states that such a transfer would only be prohibited "if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture" is vague, and shifts the burden of proof to the public health official to demonstrate such a case.

1) Recommendation

Strike the phrase "beyond that which occurs by natural genetic exchange" in I-D-3.

Strike the phrase "that are not known to acquire it naturally" in I-D-5.

Delete the remaining phrase "if such acquisition could comprise..." and replace with "except when the researcher can document that such acquisition would not compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture."

C. The exemption given to certain species which are known to exchange DNA molecules in nature, (Sec I-E-4) includes known human pathogens (i.e. Shigella, Salmonella, Klebsiella and Pseudomonas species). In exempting them from meeting all requirements of the NIH guidelines, a false sense of security may be generated. Certainly, the attempt here was not to imply that normal laboratory safeguards employed in handling such organisms were not to be circumvented.

1) Recommendation

Add the necessary specification in Sec I-E-4 on page 33070 that reminds the researcher that laboratory procedures appropriate to the known pathogenicity of such organisms must still be followed.

I hope that these remarks augment your review process and may be assessed along with the other comments you will be receiving to make the final guidelines reflective of the full range of individual expertise and concern which you have solicited.

Sincerely,

Marc Lappe

Marc Lappe', Ph.D., Chief
Office of Planning and Evaluation

cc: Pam Lippe
Susan Wright
Jon King
Leslie Dach
James Chin
Ed Lennette

Columbia University in the City of New York | New York, N.Y. 10027

OFFICE OF PROJECTS AND GRANTS

Box 20 Low Memorial Library

212 280-3023

August 24, 1978
OPG:L:8719

Dr. Donald S. Frederickson
Director
National Institute of Health
Bethesda, Maryland 20014

Dear Dr. Frederickson:

I write to obtain your publication "Laboratory Safety Monograph - A supplement to the NIH Guidelines for Recombinant DNA Research" which was announced in the Proposed Revised Guidelines for Recombinant DNA Research in the Federal Register of July 28, 1978.

Speaking generally, and without the specific comments of our Institutional Biosafety Committee, I applaud your efforts in reshaping these regulations. There would be less control of research now known to be safe, and more sensible control of that research covered with larger amounts of that control resting in the hands of the Universities.

Sincerely yours,

James P. Lewis

James P. Lewis
Director

sr

NEW ENGLAND MEDICAL CENTER HOSPITAL

The Clinical Unit of the Tufts-New England Medical Center

Uniting the Boston Dispensary, Boston Floating Hospital for Infants and Children, and Pratt Clinic-New England Center Hospital

171 Harrison Avenue, Boston, Massachusetts 02111 Area code 617 956-5000

August 25, 1978

Donald S. Fredrickson, M.D.
Director, National Institutes of Health
Public Health Service
Department of Health Education & Welfare
Bethesda, Maryland 20014

Dear Dr. Frederickson:

I wish to comment on the Proposed Revised Guidelines for recombinant DNA research issued on July 28, 1978. As you know, the issue of risk assessment was considered at the Falmouth Conference in June, 1977, and as Chairman of this meeting, I had the opportunity to carefully review the potential dangers of such research endeavors. The proceedings of the conference, which was published in the Journal of Infectious Disease this year, recognized that many of the earlier fears concerning recombinant DNA research were unfounded, based on new experimental evidence which had accumulated.

It is my view that the Proposed Revised Guidelines have incorporated the essence of the Falmouth meeting with regard to plasmid research, as well as other information which has become available concerning phage vectors. As a result, I feel that the proposed guidelines represent a reasonable and sound approach for future research with recombinant DNA molecules. These guidelines still recognize the areas of doubt, about which we need more information, but have altered in a sensible manner the requirements for experiments which are now considered safe to investigators and the public at large. For these reasons, I would lend my strong support to acceptance of this document as the policy for all NIH-supported or -conducted research with recombinant DNA molecules.

Sincerely yours,

S. L. Gorbach

Sherwood L. Gorbach, M.D.
Chief, Infectious Disease Section
Professor of Medicine & Microbiology

SLG/jel

FREDERICK CANCER RESEARCH CENTER

P.O. BOX B ■ FREDERICK, MARYLAND U.S.A. 21701 ■ 301 663-8000

August 25, 1978

Dr. Donald S. Fredrickson
Director, National Institutes
of Health
Building 1 Room 124
Bethesda, Maryland 20014

Dear Dr. Fredrickson,

We want to commend you and the recombinant DNA advisory committee on the proposed revision of the guidelines. We find that they represent a more realistic assessment of the potential dangers involved in recombinant DNA experiments than that made in the original guidelines. Accordingly, certain experiments are now exempt from the guidelines while both physical and biological containment requirements have been reduced to more appropriate levels. Furthermore, the review and approval of projects by the Institutional Biosafety Committee (with the exception of those requiring P4 containment) should eliminate many of the unnecessary delays that have occurred in the past.

We would like to propose that the new guidelines should allow the substitution of the P3-EK1 containment level wherever the P2-EK2 containment is specified (e.g. in the shotgun cloning of mouse DNA in prokaryotic vectors). The requirement for EK2 containment eliminates many of the genetic tools that are employed for selection and characterization of cloned restriction fragments.

With the exception of the change mentioned in the preceding paragraph, we would like to express our support for the proposed revision and acknowledge our appreciation for all of the work that you and the recombinant DNA committee have done. We remain

Respectfully yours,

Michael Yarmolinsky

Michael Yarmolinsky

Robert Yuan

Robert Yuan

Nat Sternberg

Nat Sternberg

Members of the Frederick Cancer
Research Center Biosafety Committee

:dmf

Litton

OPERATED FOR THE NATIONAL CANCER INSTITUTE
BY LITTON BIONETICS, INC.

University of Hawaii at Manoa

Cancer Center of Hawaii
Basic Science Unit
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Office of the Director

August 25, 1978

Dr. Donald S. Frederickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Frederickson:

I appreciate being sent a copy of the Proposed Revised Guidelines for Recombinant DNA Research, and also being asked for my comments on the proposed revisions. In general, I am glad to see that the containment requirements for these experiments are being revised to conform more closely to present estimates of the risks involved, i.e., little or none. However, I fear that the revised guidelines fail to remedy some of the more serious problems in the present system, and it is for this reason that I am writing these comments, in response to your invitation.

It has been said that there are two types of hazards associated with performing recombinant-DNA experiments. The first type, which is what everyone talks about, is the biological hazard from the organisms themselves. These hazards are purely hypothetical, and in most cases, are not likely to exist. The second type of hazard, however, is very real--the tangle of bureaucratic regulations and red tape which has come to ensnarl this research, largely because of what are now seen as misconceptions in early estimates of possible biological hazards. Over the past two or three years, the public perception of the possible risk from recombinant-DNA work has relaxed considerably, as new knowledge has emerged and no evidence of hazards has been uncovered; in the same time period, however, the bureaucratic requirements for documents reporting such experiments have escalated. In addition, since no mention of "MUA's" or any of the other rules appears in the original guidelines, the requirements imposed have frequently seemed arbitrary, ambiguous, and confusing. This has led to such situations as the recent one at Harvard, in which no threat to public health or safety was at issue, but which has made everyone involved look bad, including the rulemakers at NIH.

AN EQUAL OPPORTUNITY EMPLOYER

My first recommendation for remedying this situation is to return to the original ideas of the conferees at Asilomar and elsewhere, and delegate the responsibility for all enforcement of the recombinant-DNA guidelines to the local Institutional Biosafety Committees (IBC's). I know, from conversations with Dr. Paul Berg, that this is exactly what he and most of the other scientists at Asilomar had in mind, rather than regulation of individual investigators from Washington. The NIH Office of Recombinant DNA Activities (ORDA) has no way of knowing, in fact, if the experiments being performed, or the facilities in use, bear any resemblance to their descriptions in the MUA. The central ORDA could use its time much more profitably in simply insuring that the various IBC's were doing their jobs satisfactorily. This would include such factors as making sure that the committee membership was adequate for its job, and receiving periodic reports from the committee on recombinant-DNA work which it was regulating. Although a system of this type would seem to be the simplest and best way of enforcing the guidelines, I do not expect it to be adopted. Experience would indicate that while the number of forms required by a government organization increases periodically, it almost never decreases. The burden of the MUA, adding little or nothing to safety but much to inconvenience, will probably be with us for a long time.

As a secondary recommendation, therefore, I would urge that you at least consider removing the most obviously unnecessary requirement in this area, namely, that a completed MUA must accompany every grant application involving recombinant DNA before the application will be reviewed. Since the majority of grant applications in this area, as any other area, do not result in a funded project, no recombinant-DNA experiments are ever performed as a result, and the time and effort which go into all these MUA's are totally wasted. Secondly, real compliance with this rule is almost never possible for new projects, for the following reasons: in order for an IBC really to be able to evaluate a proposed project, they must have the completed grant application before them. However, it is well known that most grant applications are not completed until just before the deadline date, and it is unlikely that the committee will be meeting at exactly that time, or even within a short time thereafter. If the MUA is submitted with the grant application, then, the thoroughness of evaluation by the IBC is somewhat questionable, at best. Finally, the review process for NIH grants has been stretched out to such interminable lengths (7 to 10 months, at best), that even if an application eventually is funded, the MUA originally submitted will be so old that a new one will have to be submitted before beginning work on the project. Most of this unnecessary effort could be avoided by requiring only that an approved MUA must be on file with ORDA before any experiments involving recombinant DNA could begin. The choice of whether to submit the MUA early, and have it approved before the activation of the grant, or to wait until a project was funded, would then be left to the investigator. This procedure would involve neither any risk to public health or safety, nor the delegation of any enforcement authority now held by ORDA.

I am sure you realize that continued compliance with the letter and spirit of the recombinant-DNA guidelines depends to a large extent on the

perception of these guidelines as fair and reasonable by the scientific community. I am encouraged in this belief by the proposed revisions in required laboratory procedures presented in these documents. However, I hope that as much attention will be paid to insuring that the requirements for reporting such experiments will also be perceived as necessary and reasonable by the scientists subject to them. I hope that these opinions will have been of some help, and I thank you for your consideration of them.

Sincerely,

Jim Bearden

James C. Bearden, Jr.
Assistant Researcher

JCB:ssh

University of Florida

J. HILLIS MILLER HEALTH CENTER
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DEPARTMENT OF IMMUNOLOGY AND
MEDICAL MICROBIOLOGY

August 25, 1978

Dr. Donald S. Fredrickson
Director, National Institutes of Health
Building 1, Room 124
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I have read the Proposed Revised Guidelines for recombinant DNA research. In my opinion they constitute a major rational step in the right direction consistent with still unresolved scientific questions. In particular I am in agreement with the revisions concerning viral genomes which do represent the best information available.

The transfer of power to decide about the level of containment required for many experiments to the local biosafety committees should significantly decrease the time involved without in any way compromising the Guidelines. I believe that local committees which are acceptable to the N.I.H. will be qualified in every way to make these decisions. Clearly communications between investigator and local committee will be easier.

In conclusion I strongly support adoption of the Proposed Revised Guidelines.

Sincerely,

Kenneth I. Berns

Kenneth I. Berns, M.D., Ph.D.
Professor and Chairman

KIB:ams

EQUAL EMPLOYMENT OPPORTUNITY/AFFIRMATIVE ACTION EMPLOYER

Charles E. Weber
141 Mt. Horeb Rd.
Warren NJ 07060
Aug. 28. 1978

Director NIH
Bldg. 1, Rm. 124
9000 Rockville Pike
Bethesda Md. 20014

Dear Sir;

I understand that hearings will be held Sept. 15, on regulations affecting recombinent genetic research. I would like to advance the concept of placing a moratorium on all recombinent research using organisms parasitic to or symbiotic with man. Also I would like to see prevented recombinations of genes which synthesize molecules which can be absorbed across intestinal or mucous membranes and which are closely similar to molecules affecting mammalian physiology. I consider such work as the most desparately dangerous undertaking ever attempted by man.

I would therefore like to recieve the information mentioned in the article which acquainted me with this hearing.

Sincerely Yours,

Charles E. Weber

Charles E. Weber

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

Department of Biochemistry, SJ-70

August 28, 1978

Dr. D. S. Fredrickson,
Director
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

I am writing this letter to urge your consideration in adding *Caulobacter crescentus* to the list of organisms which are exempt from the NIH Recombinant DNA guidelines.

I have been in contact with Dr. Bert Ely regarding this matter, since his laboratory is primarily concerned with the development of the *Caulobacter* genetic system. It has been my understanding that the efficient intergeneric transfer of genetic material under "optimal laboratory conditions" has been demonstrated in *Caulobacter*. Transfer of RP1 to *C. crescentus* was initially demonstrated by Alexander and Jollick (1977) and Dr. Ely and his laboratory have demonstrated the transfer of other P-type plasmids and colE1 to *C. crescentus*. Dr. Ely has also provided me with a preprint of a manuscript submitted to *Genetics* which provides well-documented evidence of:

1. the transfer of RP4, RK2, R68.45, R702 and R46 from *E. coli* to *C. crescentus;*

2. expression of drug resistance to tetracycline and kanamycin mediated by RP4. Additional evidence of RP4 expression in *C. crescentus* was provided by the demonstration that *C. crescentus* containing RP4 produce RP4-type pili and are subsequently sensitive to RP4 sex pilus-dependent phage;

3. RP4 mobilization of colE1 transfer to *C. crescentus*. However, ColE1 in *C. crescentus* can be maintained and expressed in the absence of RP4;

4. RP4 mobilization of chromosome transfer between *C. crescentus* and *E. coli* (either direction);

5. the insertion of transposable element Tn 7 in the *C. crescentus* chromosome.

J405 Health Sciences Building, SJ-70 / Telephone: (206) 543-1660

It is my further understanding that *Caulobacter* was excluded from the new guidelines because of a lack of published material concerning the above-mentioned experiments describing intergeneric exchange. Dr. Ely's manuscript describing this data has been submitted. In my opinion, after careful review, the manuscript appears to be well-documented and contains nothing which should impede its speedy acceptance and subsequent publication. It is my further understanding that intergeneric exchange in some of the organisms already included in the revised guidelines, *Agrobacterium* for example, is not as extensively described as that for *C. crescentus*.

I hope that you will find it possible to review the data and add *Caulobacter* to the new guidelines as it will substantially facilitate research which by all available criteria should be exempt under the proposed revision of the NIH guidelines on recombinant DNA.

Very truly yours,

Nina Agabian

Nina Agabian
Associate Professor

NA:kg

Baylor College of Medicine
DEPARTMENT OF VIROLOGY AND EPIDEMIOLOGY • 713 790-4443

August 28, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I have been asked to send you my opinion about the virological aspects of Guidelines on Recombinant DNA Research, published July 28, 1978, in the Federal Register.

I am in agreement with the Report (Appendix F of the above) of the Virus Working Group which met at the NIH on April 6-7, 1978. Because of a private lecture and consultation trip sponsored and paid for by the Chinese Academy of Medical Sciences, I regret that I could not attend the meeting of the Working Group mentioned above. For your interest, I visited a laboratory in Shanghai that was being established for Recombinant DNA work.

As you know, I feel that containment is a problem that is not new to responsible investigators dealing with infectious diseases and their causative agents. There is no substitute for proper techniques, either to prevent contamination of the isolated agent, or to protect laboratory personnel. Perhaps all who set out to conduct Recombinant DNA Research should be examined and certified as qualified to work with infectious agents.

The one note of caution that I would offer relates to the concept that organisms which carry viral DNA inserts are of no hazard to the community; while potential hazards remain an unlikely possibility, no definitive proof exists to rule them out completely. To my knowledge higher or lower animals have not yet been exposed to such organisms carrying viral DNA segments. Recombinant DNA could possess biological activity (for example, in some cases viral DNA segments linked to heterologous DNA sequences can become integrated into the genome of animal cells), and exposure to large amounts of such material might lead to unexpected results.

With kind regards,

Sincerely yours,

J. L. Melnick/ce

Joseph L. Melnick
Distinguished Service Professor

(dictated but not read)

TEXAS MEDICAL CENTER • HOUSTON, TEXAS 77030

THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Division of Health Affairs
The School of Medicine
Department of Bacteriology and Immunology

The University of North Carolina at Chapel Hill
804 Faculty Laboratory Office Building 231H
Chapel Hill, N.C. 27514

August 29, 1978

Dr. Donald S. Fredrickson
Department of Health, Education and Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Although I am a scientist who was until recently only passively interested in the new recombinant DNA technology, I have welcomed the cautious approach taken by the government in establishing appropriate guidelines for investigators who wish to perform these experiments. In fact since the guidelines first appeared I have seen my own research area rapidly develop into one where the recombinant technology can be extremely useful. I have also followed with concern the criticisms of many oponents to this type of research.

I have recently studied the proposed revisions of these guidelines and am writing to express my wholehearted approval. I appreciate the fact that there will be guidelines and that known hazardous experiments will be restricted to appropriate research facilities but that the revisions will not become obstacles to interfere with simple manipulation with recombinant molecules or to the advancement of science. Please register my complete support of the revisions and accept my personal thanks for the tremendous contribution you have personally made toward the advancement of science by over-seeing the drafting revision and re-revision of the guidelines.

Sincerely yours,

Kenneth F. Bott

Kenneth F. Bott
Associate Professor

AREA CODE 608
PHONE 262-2177

MEDICAL CENTER

McARDLE LABORATORY
FOR CANCER RESEARCH

UNIVERSITY OF WISCONSIN · MADISON, WISCONSIN 53706

August 29, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Building 1, Room 124
Bethesda, Maryland 20014

Dear Doctor Fredrickson:

I read carefully the Proposed Revised Guidelines (Federal Register 43, 1978, pp. 33069-33095) and I have three kinds of comments.

1. These Guidelines are clearly superior to the 1976 Guidelines and should be rapidly approved by you, after modifying slightly as specified below and in the enclosure.

2. There is one great inconsistency in the Proposed Guidelines which could easily be corrected. At the end of column 1 on p. 33070 the following sentence should be added: "All other experiments employing the recombinant DNA technique are not prohibited when conducted as specified in the following sections; whenever a specification is not provided, they should be conducted under P2 containment or containment specified by the local IBC or ABC".

   This addition is very important since otherwise a large class of "inadvertently prohibited experiments" is created which were never intended to be prohibited and which could be excepted only after a lengthy process similar to that for the I-D Prohibitions. For instance, all experiments for which no HVI vector was as yet approved (which takes often over a year) are "inadvertently prohibited" even if they do not present any risk, as e.g. cloning genes coding for colicins (E. coli antibiotic) in a Streptomyces-bacteriophage host-vector system.

   This is clearly a very serious omission and must be corrected since otherwise the Guidelines would de facto prohibit many classes of completely harmless and very beneficial research (including studies on the synthesis of antibiotics), and thus clearly violate all original intents as related to safety. Clearly, it is not the mission of NIH to prohibit or hinder and delay beneficial medical research.

   Another important change is to modify line 4 in the second column on page 33070 to read "...described in sections I-D-1 to I-D-3 as being...". Sections 4, 5 and 6 do not apply to Exemptions.

   These and other suggestions for minor revisions and corrections of typographical errors are enclosed.

3. The Guidelines have become an extremely complex legal document, the complexity of which bears no relationship to the hypothetical risks they are supposed to control. The damage caused by the Guidelines greatly outweighs their benefits, if any. This damage created by the regulations includes (1) creating novel or aggravating existing hazards, (2) political dangers, (3) depleting and misdirecting valuable resources, (4) fostering bureaucracy, (5) denying or delaying benefits to society, and (6) misdirecting environmental concerns and other beneficial measures, as described in the enclosed article (W. Szybalski, Dangers of Regulating the Recombinant DNA Technique, Trends in Biochemical Sciences, November 1978).

   It is also clearly stated by your Deputy Director Dr. DeWitt Stetten (published in Gene 3, 1978, pp. 265-268) "that regulation is antithetical to creativity, and ... that the best regulation for the flowering of science is the least regulation..." I also concur with his proposal that the NIH Guidelines should be replaced by a very simple statement, e.g., "The conditions of containment appropriate for any recombinant DNA experiment are those which are dictated by the most virulent or dangerous organism entering into that experiment".

I strongly implore you to start prompt action leading to abolishing the unnecessary, bureaucratic and complex Guidelines and replacing them with some simple (one sentence or one paragraph) statement indicating that any recombinant DNA activities involving use of pathogenic organisms should be done with proper precautions and prudence. The time is ripe for such action and I am sure that your forsight and courage will lead to a successful conclusion of this rather infamous chapter in the history of the biomedical sciences.

With the warmest personal regards,

Sincerely yours,

Waclaw Szybalski

Waclaw Szybalski
Professor of Oncology

WS:kjd

THE JOHNS HOPKINS UNIVERSITY
SCHOOL OF MEDICINE

DEPARTMENT OF MICROBIOLOGY

725 N. WOLFE STREET
BALTIMORE, MARYLAND 21205

August 30, 1978

Dr. Donald S. Frederickson
Director, NIH
Bethesda, MD 20014

Dear Dr. Frederickson:

I am responding to your request for comments on the proposed revised guidelines for recombinant DNA research, dated July 19, 1978. First, in general terms, I believe the revisions accurately reflect the experience with recombinant DNA of the past four years and the considered judgements of risk of infectious disease experts, whose input was unfortunately lacking initially. In my opinion revised guidelines will allow important advances not possible under the present rules. Second, I find the increased emphasis on the responsibility of local biosafety committees in carrying out the guidelines a very important and appropriate change. At Johns Hopkins University the local committee has been functioning very effectively, whereas the need to obtain NIH approval of each project has caused delays without, I believe, adding to the project's safety. Another constructive change in the guidelines is the provision for case by case consideration of unanticipated situations such as development of new vectors. I hope the mechanism for review of these proposals can be simplified by separating out for prompt action those that represent relatively minor extensions of the guidelines.

Finally, I would like to make a specific comment on animal virus vectors. I served on the (American) working group that drafted the early recommendations, and of course approved them. However, I now notice an unintended practical restriction on the use of human adenovirus as a vector, namely the requirement that it "... be rendered unconditionally defective by deletion of at least two capsid genes ..." (III C-1-c-(1)-(a) p. 33081). Recently it has been possible to isolate deletion mutants of adenovirus that grow only in adenovirus-transformed cells, i.e., the "helper virus" is the integrated transforming segment. To allow this host-virus system to be used for isolating adenovirus-foreign DNA recombinants, I suggest that III-C-1-c-(1)-(a) be clarified to read as follows:

"Human adenoviruses 2 and 5 rendered unconditionally defective by deletion of at least two essential genes, with appropriate helper, can be used in P3 conditions to propagate DNA sequences from:"

Thank you for the opportunity to comment on the revised guidelines.

Sincerely,

Daniel Nathans

Daniel Nathans
Professor and Director
Department of Microbiology

DN/lc

HOFFMANN-LA ROCHE INC.

NUTLEY • NEW JERSEY 07110 • TELEPHONE (201) 235-5000 • (N.Y.C.) 695-1400

RESEARCH DIVISION

August 30, 1978

Dr. Donald S. Frederickson, Director
National Institutes of Health
Bethesda, Maryland

Dear Dr. Frederickson:

In consideration of the Federal Register announcement of July 28, 1978, I wish to urge that experiments involving recombinant DNA technology be permitted in species of the genus Streptomyces. This group of microorganisms has an enormous importance in the production of antibiotics, the strains can be handled without presenting a hazard to human health, and genetic exchange has been demonstrated among several species of the genus. Recombinant DNA experiments could in the near future add a new dimension to the methodology for strain improvement.

Sincerely yours,

N. J. Palleroni

Norberto J. Palleroni,
Curator of the Microbial Collection
Chemical Research Division

NJP:rlb

THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Division of Health Affairs
The School of Medicine
Department of Bacteriology and Immunology

The University of North Carolina at Chapel Hill
804 Faculty Laboratory Office Building 231H
Chapel Hill, N.C. 27514

August 30, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

In the absence of any documentable evidence or consensus within the scientific community that recombinant DNA research poses a hazard to society I find the entire concept of Research Guidelines repugnant. The new proposed Guidelines continue to restrict research and greatly reduce the output of recombinant DNA researchers. In as much as there is a small reduction in the outrage embodied in the proposed Guidelines they represent a tiny step in the right direction. We need many more such steps.

Sincerely,

Marshall Hall Edgell

Marshall Hall Edgell, Ph.D.
Professor

Apartado 8-4480
San José, Costa Rica
August 30, 1978

Director
NIH
Building 1, Room 124
9000 Rockville Pike
Bethesda, Maryland 20014
USA

Dear Sir:

I am responding to your invitation to make comments on proposed revisions to the NIH Guidelines on research involving recombinant DNA molecules.

I am Mrs. Average Citizen with no scientific qualifications whatsoever to judge or to criticize the proposed guidelines. As such, then, my overriding interest is in the safety of the proposed experiments and the protection from "mistakes", accidents, or "unexpected developments" that DNA ressarch may entail. I believe in the closest government control and supervision of this research. My opinion is that all parties - private and public - involved in DNA research must be supervised and controlled by adecuate government regulations and supervisory structure. There must be no possibility from any party of a "Pandora's Box" from DNA research.

I would not allow the scientists alone to set up standards and guidelines for the supervision of DNA research. Barbara Villet in her article in the ATLANTIC (June, 1978), "Opiates of the Mind", in writing about scientists writes: "When word of this find [scientific] reached the United States, it was received with a mixture of excitement and dismay. 'It meant they were ahead of us in the race,' Avram Goldstein recalls, 'and science is just that - a race. It's cooperative, but it's competitive too, and probably more of the latter because scientists are by nature competitive people. Since there isn't much in the way of monetary rewards for what they do, they go for the ego rewards.' "

At all costs DNA research must go ahead - if at all - at a slow, controlled pace so that the welfare of the people will not be sacrificed to the ego rewards in "the race" of scientists involved in this kind of research.

Very truly yours,

Jean P. Patterson

Mrs. Chester A. Patterson, Jr.

cc: Senator Kennedy

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
77 MASSACHUSETTS AVENUE
CAMBRIDGE, MASSACHUSETTS 02139

DEPARTMENT OF BIOLOGY

PHONE: (617) 253-1000

August 31, 1978

Dr. Donald S. Fredrickson
Director
Department of Health, Education, and Welfare
Public Health Service
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

I am responding to the request for comments on the proposed revised guidelines on recombinant DNA research.

I am pleased that there has been so much discussion and careful assessment by the scientific community, our senators and representatives, and the general public. The problem has been well aired, and I believe that the scientific community has been particularly conscientious in weighing the issues involved. Because of this, I feel that the proposed revisions carry the weight of reasoned judgement and sincerety, without the taint of self-serving prejudices.

Since I am closest to the bacterial cloning work, where the inserted DNA is derived from bacteria, I have concentrated most on the revisions pertaining to this. I believe it is entirely appropriate that much of this work be placed into a declassified status. Thus, whether the source of the DNA is E. coli, λ, or even an attenuated strain of S. typhimurium, I believe that declassification is appropriate. This will certainly make work in this area more efficient, and in a general sense less costly, without any apparent attendant increase in hazard.

I hope these comments are of some use, and I hope that the public hearing on the proposed revisions will be fruitful.

Sincerely yours,

Paul R. Schimmel

Paul R. Schimmel
Professor of Biochemistry and Biophysics

PRS/jm

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August 31, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, MD 20014

Dear Don:

Thank you for your letter of July 24. I have read the proposed guidelines for recombinant DNA research especially those portions dealing with animal viruses and cells, an area in which I have expertise.

I regard the guidelines dealing with the cloning of animal viruses and eukaryotic genomes into E. coli K12 as reasonable. I do not believe that any harm can come from experiments carried out as described in the guidelines. In fact, I wonder about the necessity of regulating these experiments at all beyond the regulations required for work with the viruses and eukaryotic genomes directly.

As our knowledge of vertebrate genomes and viruses increases, we are finding fundamental differences between them and E. coli. These differences make it even less likely than was previously believed that the viral or vertebrate genes can be expressed in E. coli unless special manipulations have been performed.

However, in respect to the use of animal viruses as cloning vectors, I still have some hesitation about the use of so many animal viruses that can replicate in and transform human cells. Clearly there is no hazard to work with these viruses in cell cultures. However, I see no reason now not to restrict this cloning work to rodent and bird viruses and cells.

Two minor points: "Genomes" is mispelled "genames". In the impact statement: I do notthink it is fair to call cloned hormones genes when they are from cDNA from a vertebrate messenger mRNA. The clone lacks all before and after and intervening sequences.

I hope that the guidelines will be promulgated in the present form or in an even less restrictive form.

With best regards,

Sincerely yours,

Howard

Howard M. Temin

HMT:kjd

ROCHE INSTITUTE OF MOLECULAR BIOLOGY

NUTLEY, NEW JERSEY 07110

August 31, 1978

Dr. Donald Fredrickson
National Institutes of Health
Building 1, Room 124
Bethesda, Md. 20014

Dear Dr. Fredrickson:

As you requested, I have reviewed the Proposed Revised NIH Guidelines for Recombinant DNA Research (published on July 28, 1978 in The Federal Register) and offer the following comments:

First, I would like to express my appreciation for the thorough and objective way in which all of the many questions and issues raised since the publication of the first revision have been addressed both in the "Decision" section and in the proposed changes. In my capacity as member of a RAC working group and as convenor of COGENE's "Working Group on Risk Assesment", I have had the opportunity to follow the many recent developments relevant to recombinant DNA research. My general impression is that the new Proposed Guidelines--although still restrictive--do much to improve administration and to adjust experimental guidelines to accommodate the experience and new knowledge accumulated over the last three years. Particularly significant has been the input from the groups of knowledgeable scientists (at Falmouth and Ascot, etc.) who have conducted technical analyses of the possible risks associated with recombinant DNA research and have made concrete suggestions as a result of their assessments. It is, of course, imperative that such analyses be employed where ever possible, so that the number of assumptions utilized in constructing the guidelines may be reduced to a minimum.

However, while I appreciate the tremendous work and effort that must have been involved in addressing the range of scientific and public opinion regarding recombinant DNA research I must, as a scientist, question the long delay in adoption of revisions. The new proposals (PRG-NIH) are undoubtedly more appropriate than those drawn up by the RAC a year ago (PRG-RAC). But even the PRG-RAC were a significant improvement over the 1976 version which experimentors in the U.S. still are obliged to follow. In comparison with many other countries, we have become so out-of-date that reputable scientists at some of our leading institutions (Harvard, University of California, Cold Spring Harbor Laboratories) have found it necessary to travel to Europe to perform experiments.

continued . . . . . .

I am in sympathy with their action, but surely it was not the intention of the Guidelines to put these elegant and simple tools of molecular biology within reach of only the well-endowed or well-connected. I share with many of our colleagues a sense of urgency that these revisions be adopted as quickly as possible and that the NIH give top priority to establishment of mechanisms which will allow the Guidelines to be more responsive to changes in the state of our knowledge.

Finally, I would like again to draw your attention to a detail in the containment guidelines for permissible experiments, which I first discussed in comments regarding the PRG-RAC (copy attached), namely, the lack of flexibility provided for "shotgun" experiments with DNA of higher eukaryotes. The present "Decision" section (p33059) quotes the 1976 Guidelines in providing two rationales for establishing containment levels for such shotgun experiments. One, the "more concrete reason" for scaling containment upward with evolution was the concern for contamination with viral DNA sequences. This, of course, is no longer applicable since in most cases the new proposals provide more flexibility for work with pure viral DNAs than with the DNAs of higher eukaryotes. What remains then are the second, less concrete "assumptions" based on the probability that a prokaryote might translate eukaryotic DNA to produce a harmful product, with the resulting concern that a "rogue" bacterium containing this gene would escape and spread in the environment. These, of course, were the very questions addressed at the Falmouth Conference. As you are aware, the participants at Falmouth concluded that the chance of an E. coli K12 host being converted into an epidemic pathogen by insertion of random bits of foreign DNA was negligible. If the "rogue" bacterium cannot be spread by virtue of pathogenicity then the relevance of this concern must surely be brought into question. Furthermore, more recent findings which show extensive modification of mRNA in eukaryotes (cites on p33047) indicate that faithful expression of eukaryotic genes in prokaryote will probably be much less frequent than first imagined. Indeed, as of this date, the only eukaryotic genes which have been found to function in prokaryotes are those of the lowest forms, i.e. yeast and Neuospora.

I note in the discussion of these shotgun experiments (p33060) that the reason given for a lack of flexibility in the case of higher eukaryotes was an "...increased confidence in the biological containment offered by the EK2 system..." While, as a member of an "EK-2-vector" RAC working group, I share this confidence, this line of reasoning hardly seems applicable. What would be applicable is a technical appraisal of the possible risks that might be associated with these experiments, using criteria similar to that applied in the establishment of other levels. As discussed above, in light of the Falmouth report and other recent findings, it is hard to imagine how any realistic assessment could conclude that the probability of inclusion of an expressed "harmful" gene in an EK-1 host would be significant enough to place these experiments at a level of containment higher than that now utilized routinely to handle concentrated cultures of true pathogens (i.e. P3). Furthermore,

continued . . . . . .

I know of no rational scientific basis on which one might predict that such inclusion and expression would be any more likely in shotguns of mouse as compared with yeast DNA.

I have discussed this seemingly minor "detail" at some length because I believe it involves several important principles. One, is that every effort must be made to base the assignment of containment levels on something better than assumption. I believe that principle has not been applied in this instance. The second, questions the advisability of setting containment guidelines which, in effect, prohibit whole classes of experiments. Upgrading from P2 to P3, makes experimentation more difficult, but does not *a priori* rule out any specific class; upgrading from EK1 to EK2 makes whole classes of experiments (e.g. those requiring bacteriophage lambda lysogenization, or those utilizing the rich genetic library of *E. coli* K12 strains) impossible. The full impact of this decision does not seem to have been thoroughly considered.

I hope that these comments will be helpful to you--and I again hope that they will encourage your advisors to reconsider these classifications. I realize that if the Guideline revisions are to be adopted on a regular basis, each issuance will be somewhat less than perfect. Although I feel obliged to bring your attention to this detail, I would like to close by emphasizing the need for rapid implementation of the proposed revisions.

Yours truly,

A. M. Skalka, Ph.D.
Department of Cell Biology

AMS:pcp

[Attachment published in *Recombinant DNA Research*, *Volume 3*, Appendix A, p. 9, September 1978.]

applied biochemists inc

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August 31, 1978

Dr. Donald S. Fredrickson, M.D.
Director, National Institute of Health
Department of Health, Education and Welfare
Building 1, Room 137
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Upon reviewing the July 28, 1978, Part IV, Federal Register on the National Institute of Health's proposed revised guidelines on recombinant DNA research, I have found the vast majority of the proposed guidelines to be most satisfactory.

The areas of the proposed guidelines that I find troublesome are the following:

1. My first comment is in reference to physical containment at level P3. It is my feeling that an autoclave should be within the controlled laboratory area, if not in the laboratory itself. As stated in the proposed guidelines on page 33073 of paragrph II-B-3-c-(6) "An autoclave for sterilization of wastes and contaminated materials shall be available in the same building (and preferably within the controlled laboratory area)..." It is not rational to have the laboratory apart from unrestricted traffic flow by a controlled access area and transport contaminated materials out of the controlled area into uncontrolled surroundings for sterilization. There exists a potential hazard and a means of contamination with the autoclave not being present in the laboratory, at a P3 level, during recombinant research.

   The cost of installing an autoclave in the laboratory should not be a decisive factor since so many other precautions must be taken at this level. It certainly would not be a double-door autoclave which is warranted at a P4 level, but it should at least be present within the laboratory to prevent a potentially hazardous situation.

   In summary, it is my suggestion that an autoclave be required in the laboratory, preferably in the controlled area, at a P3 level. The level of potentially hazardous conditions do not warrant P4 level practices and containment, but do warrant tighter restrictions than a P2 level. Thus, the paragraph should

read, "An autoclave for sterilization of wastes and contaminated materials shall be available in the laboratory (and preferably within the controlled laboratory area)..."

2. An area of great concern and debate are the restrictions and prohibition of the release of an organism containing recombinant nucleic acid structures. As of this time, the guidelines prohibit such action and with due cause. The release of a recombinant organism without sufficient efficacy and environmental assessment may be hazardous to other free-living organisms and the environment, providing it is able to survive in a given niche. With this in view, there still exists sufficient reasons that warrant the release of said organisms, providing there exists efficacy, an environmental assessment, and sufficient rules and regulations to protect against a potentially hazardous organism or the development of a mutation of the same.

   The development of certain organisms with an ability to carry out useful functions, both for industry and the environment, should be sought. The regulations for the release or use of these organisms should be developed. These regulations must insure that there is sufficient research, environmental assessment, mutagenic studies, and other related studies in order to safely warrant the release or use of beneficial recombinant organisms.

   The guidelines make no provision for such activities, nor is it apparent that it will in the near future. I feel such activities should be made available.

   There is no question that there is a lack of information concerning hosts, vectors, and recombinant organisms. There are many risks when dealing with this research. Thus, precautions must be taken to protect nature from such risks. But, if a beneficial organism to industry and the environment is developed with the proper efficacy, regulations, and assessments, it should be utilized.

   Proper legislation should be set forth to allow for the possible usage of recombinant organisms. Section 361 of the Public Health Service Act is a major piece of legislation that may provide for commercial applications. New legislation, with future developments in mind, is needed to cope with this problem.

   In summary, I recommend that the possibility of utilizing a recombinant organism be made available through regulations set forth by the National Institute of Health, the Food and Drug Administration, Section 361 of the Public Service Act; and possible future Congressional legislation. The possible benefits are all too great to ignore, providing there exists strict control.

There are many more issues that one could expound upon, both administratively and technically. Recombinant DNA research is still in an infant state and the guidelines are bound to be fallible. There will be mistakes, additions, and deletions. One can only foresee the implications and results, and control thse aspects through due process. The purpose of my second comment is to make one more aware of the needs of the future and what must eventually be.

I am satisfied with the technical aspects of the guidelines. The proper measurements of safety have been taken in order to carry out successful research. This will be based upon how well the researchers are trained with the guidelines as a means of standardization. Hopefully, this will serve as a base for future federal regulations in order to provide safe, and yet efficient research.

Sincerely yours,

Michael J. DiMario
Administrator, Research & Development

MJD:et

United States Department of the Interior

OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20240

SEP 1 1978

In Reply Refer To:
ER-78/757

Dr. Donald S. Fredrickson
Director, National Institutes of Health
Public Health Service
Department of Health, Education
and Welfare
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

We have reviewed HEW's proposed revised guidelines for Recombinant DNA Research, as published in the Federal Register, July 28, 1978, per your request of August 1, 1978, and we have no substantive comments on these revised guidelines.

Sincerely,

Bruce Blanchard

Bruce Blanchard, Director
Environmental Project Review

The Joseph and Rose Kennedy
Institute of Ethics

Georgetown University
Washington, D.C. 20057

202/625-2371

September 1, 1978

Dr. Donald S. Frederickson
Director
National Institutes of Health
Building One
Bethesda, Maryland 20014

Dear Dr. Frederickson:

I am writing in response to your request for comments on the most recent revision of the NIH Guidelines for Recombinant DNA Research [Federal Register 43 (146): 33042-33178, 28 July 1978].

Several researchers have recently indicated their interest in developing alternative host-vector systems to *E. coli* K-12. Among the proposed systems are the following:

Bacillus subtilis
Yeast
Neurospora
Salmonella
Pseudomonas.

Under the proposed revised guidelines published on July 28, 1978, self-cloning experiments involving any of these hosts would be exempted. However, prior to any use of these organisms as host-vector systems, they would, according to the current revision, need to be certified as HV-1 systems.

The current requirements for HV-1 systems are (1) low levels of survival of the vector in its host outside the laboratory and (2) low levels of transmission of the vector from the propagation host to other

nonlaboratory hosts. Any proposed system must fulfill both requirements.

As a non-scientist, I am not competent to comment on the adequacy of these two biological-containment requirements or on the potential or lack of hazard in any of the proposed alternative host-vector systems. From a procedural standpoint I am concerned that the current requirements for HV-1 certification may be insufficiently flexible to respond to new scientific developments, some of which may provide an even greater measure of safety than the EK systems.

There are at least two ways in which this flexibility could be incorporated into the guidelines during the present cycle of revision. The first would be to reconceptualize the two requirements for HV-1 certification as criteria. With this approach, both criteria would always be taken into account, but not every certified host-vector system would need to fulfill both criteria. For example, the survival of baker's yeast hosts and vectors in their natural habitat might not constitute a biohazard, if one were certain that the DNA contained in those hosts and vectors would not be transmitted to other cells or organisms.

A more general approach would be to build into this revision of the guidelines a procedural mechanism for minor or partial revisions of the guidelines in the future. What I have in mind is a six-month cycle in which a revision would be discussed and drafted at one meeting of the NIH Recombinant Advisory Committee (RAC), published in the Federal Register for written comment, reassessed at the next RAC meeting in light of the written comments and oral public comments made at the meeting, redrafted by NIH staff in light of the public comments and Committee recommendations, and published in final form in the Federal Register approximately six months after the beginning of the revision process. With this procedure minor deficiencies in the guidelines could be rectified without the time investment required for comprehensive revision.

Sincerely yours,

LeRoy Walters

LeRoy Walters, Ph.D.
Director, Center for Bioethics
Kennedy Institute

LW:mt

CC: Dr. William Gartland
Dr. Jane Setlow

Baylor College of Medicine
DEPARTMENT OF CELL BIOLOGY • 713 521-4701

September 1, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20016

Dear Dr. Fredrickson:

I have received a copy of the Proposed Revised Guidelines for Recombinant DNA Research (Federal Register 43, 33042-33178) and I would like to question the following.

The proposed containment for shotgun recombinant DNA work on non-primate mammals and birds is P2 + EK2, yet for cold-blooded animals, plants and many of the RNA and DNA viruses it is P2 + EK2 or P3 + EK1. Is there a sound scientific basis for not also allowing non-primate and bird recombinant DNA work to be also carried out under P3 + EK1? The restriction to the use of only P2 + EK2 is not a trivial point, since many experiments using EK1 vectors are extremely difficult, indeed some simply impossible (e.g., those involving lysogenic λ systems) in an EK2 system. In particular, I find it difficult to see why segments of some transforming viruses may be cloned under P3 + EK1 conditions, yet DNA from a non-primate mammal or bird in which any one sequence is diluted out at least one in 10^5 with the other sequences present cannot be carried out under these same conditions.

It would be greatly appreciated if you could bring this suggestion to the attention of the Advisory Committee.

Sincerely yours,

Bert W. O'Malley

Bert W. O'Malley, M.D.
Professor and Chairman

/gbc

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STANFORD UNIVERSITY MEDICAL CENTER

DEPARTMENT OF GENETICS

September 2 , 1978

Donald S. Fredrickson, M.D.
Director
National Institutes of Health Bldg.
Room 124
Bethesda, MD 20014

Dear Don:

While the proposed revised recombinant DNA guidelines are in many respects an improvement over the earlier version, I believe that they are still far too restrictive with regard to non-E. coli prokaryotic host-vector systems. Specifically, I am most concerned about the new guidelines' virtual prohibition of the use of non-pathogenic HVI systems other than E. coli K12 without extensive review and explicit approval by the NIH Recombinant DNA Advisory Committee.

As I have written previously, the HVI section of the new guidelines will bring to a halt a wide variety of experiments with non-E. coli systems that have been permitted under the old guidelines; many such experiments have been going on several years with no indication whatsoever of hazard. Some of the experiments that will be halted involve the use of gene manipulation to produce medically important products such as antibiotics. I believe that this outcome is contrary to the public interest.

The problem can be remedied by a simple sentence in the guidelines stating that experiments with non-pathogens that involve introduction of genes derived from other prokaryotic organisms within etiologic agent class I can be carried out under P2 (or P3 if you prefer) containment conditions. While this wording would establish a level of physical containment that I believe is far more stringent than necessary for safety, at least it would set forth some conditions for carrying out the experiments. Under the present wording, simple experiments involving introduction of genes from non-pathogens into other non-pathogenic non-E. coli hosts are prohibited; it does not seem reasonable to effectively place such experiments, which most scientists would agree are among the safest of all, in the "too dangerous to be done" category---while at the same time relaxing containment for almost all other recombinant DNA work.

I know that you have considered this matter in the past and have decided against implementing my recommendation. Nevertheless, I hope that this letter may prompt you to give some additional thought to the incredibly inappropriate and inequitable wording of the HVI section of the revised guidelines. With best wishes,

Sincerely yours,

Stan

Stanley N. Cohen, M.D.
Professor of Medicine and
Professor of Genetics

SC:TA

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HARVARD UNIVERSITY
THE BIOLOGICAL LABORATORIES

16 DIVINITY AVENUE
CAMBRIDGE, MASSACHUSETTS 02138

September 5, 1978

Dr. Donald S. Fredrickson, M.D.
Director,National Institutes of Health
Bethesda, Md. 20014

Dear Dr. Fredrickson:

I received a copy of the Proposed Revised Guidelines for recombinant DNA research. I would like to convey my strong feeling that the proposed revisions are appropriate alterations in the existing Guidelines, and that they represent reasonable standards by which recombinant DNA research can be conducted safely and efficiently.

I sincerely hope that the proposed revisions will be speedily approved.

Sincerely,

Nancy Kleckner

Nancy Kleckner

Assistant Professor, Department of Biochemistry
and Molecular Biology

THE ROCKEFELLER UNIVERSITY
1230 YORK AVENUE · NEW YORK, NEW YORK 10021

September 5, 1978

Dr. Donald Fredrickson, Director
National Institutes of Health
Bldg. 1 Rm. 124
Bethesda, MD 20014

Dear Don:

It must be apparent to all but the most stubborn observers that the great promise of research with recombinant DNA has been and continues to be fulfilled. Numerous significant advances in our knowledge of basic biology have been made. Sooner than expected directly useful products will be available. However it is not my purpose to tout these advances. The recent literature abounds with them. Rather I'm writing to support the immediate promulgation of the PRG for this work so that the work may proceed in the most efficient and flexible manner.

These PRG's for recombinant DNA research are obviously the result of most diligent and expert considerations. I am particularly pleased to see that the process, begun four years ago, is moving forward. Those of us who were involved in these initial discussions of recombinant DNA envisaged a continuing peer review process in which containment levels for particular experiments would be determined by the best current scientific knowledge. The reports of the expert committees were not only thorough in justifying the recommended containment levels but are also little gems of more generally useful scientific information.

Two points in the PRG are particularly noteworthy,the exemptions and the new responsibilities of the I.B.C. The clear exemption of free recombinant DNA from the guidelines is a considerable step forward. Not only does this facilitate the manipulations needed to characterize DNA study by electron microscopy, restriction enzyme cleavage, etc., but it also recognizes the fact that DNA itself is not in any way a "toxic" substance. Unfortunately, the idea that DNA functions only as heredity information has been difficult to explain. In my own experience audiences and reporters exhibit considerable surprise that E.M. pictures of Rec-DNA look just like any other DNA. Being able to cite the PRG on DNA will help.

The exemption for self-cloning and E. coli related microorganisms are also a welcome addition. There should have been such a category from Asilomar onward. Few can maintain that such experiments had any potential, conjectural or other level of hazard. Cloning coliphage lambda and putting it back together or inserting

THE ROCKEFELLER UNIVERSITY
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coli DNA into it represent a class of the most benign but useful types of experiments. The principle of the containment label matching the most potentially hazardous component should apply here as well as in the rest of the Guidelines. No potential danger, no special containment. The absence of this null category has in the past clouded the public discussions. Despite the graded series of containment levels, recombinant DNA research was visualized as one thing. Thus if hazard was assumed to be associated with any of its parts, e.g. forbidden experiments, it was all hazardous.

The new duties of the I.B.C. will make the Guidelines a bit more like guidelines and less like rules. As the Guidelines note, it can't anticipate every experiment and neither can any investigator. Basic research moves in erratic directions because its data base is continuously changing. New information, ideas and techniques suddenly appear. Hence experimental approaches are modified, dropped and new ones initiated. A distantly approved MUA tends to codify one approach. Were the Guidelines really guidelines most amended MUA's wouldn't be needed; new approaches generally fall into the category previously approved. Under the new system it would require only a meeting of the I.B.C. to certify moving in the newly logical direction.

However this authority for the I.B.C. must be viewed as a mixed blessing. As with any local authority, extraneous considerations may enter the decisions. Given a strong I.B.C. some colleagues will have authority over the research of other colleagues and opportunities for mischief may exist. It would be helpful if a review-appeal mechanism by the ORDA and RAC were written into the Guidelines.

In sum, all of those involved in the preparation of the PRG should be commended for their attention to principle and detail. I find little to fault in the technical aspects and find that the procedural aspects are not only generally appropriate but are also much less ambiguous that those of the current guidelines.

I strongly recommend that the PRG be approved as soon as possible so that the work may proceed with as little hassle as possible.

Sincerely yours,

Norton

Norton D. Zinder

NDZ:bc

MASSACHUSETTS INSTITUTE OF TECHNOLOGY CAMBRIDGE, MASSACHUSETTS 02139
Center for Cancer Research Room E17-529B

September 6, 1978

Dr. Donald S. Fredrickson
Director
Department of Health, Education and Welfare
Public Health Service
Natinal Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson,

It has recently come to my attention that the revised guidelines which should become effective this fall have restricted cloning of primate DNA in bacteria at the P2-EK2 level and have not included the option of P3-EK1. This arbitrary decision will seriously delay or block several significant experiments; particularly in the area of expression of human genes in bacteria. An example of a life saving development which this decision would seriously delay would be the creation of a bacterial strain which produces human interferon. I know this ruling will force such research out of the USA and from under the jurisdiction of the guidelines. Ultimately the USA public will have to pay for the development of such drugs in firms held by foreign counties.

I hope this can be changed before the revised guidelines are finally issued. However, if this is not possible, it is essential that rapid flexibility be built into the new guidelines. For example, it should be possible for one committee to grant exceptions to the guidelines and for the exceptions to be immediately effective.

With such flexibility it might not be necessary to continuously revise the total guidelines. This would save the expense of frequently issuing new guidelines.

Sincerely yours,

Phillip A. Sharp

Phillip A. Sharp
Associate Professor

PAS/ms

CALIFORNIA INSTITUTE OF TECHNOLOGY

PASADENA, CALIFORNIA 91125

DIVISION OF BIOLOGY 156-29

September 6, 1978

Donald S. Frederickson
Director
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Frederickson:

I would like to comment on the proposed revised guidelines for recombinant DNA research published in the Federal Register on July 28, 1978. As a researcher conducting experiments which involve recombinant DNA procedures I view the proposed revisions as a significant improvement over the present guidelines. The shift of decision-making responsibilities to local Biohazard Committees and the reduction in containment requirements for several classes of experiments will enchance the effective use of recombinant DNA techniques in basic research without posing a threat to public safety. It is my opinion that the relaxation of containment requirements are justified by the state of our understanding of the potential biohazards of recombinant DNA experiments. No hazards have been demonstrated, and the possibility of converting E. coli K12 to an uncontrollable pathogen appears exceedingly unlikely.

The research in my laboratory will be affected directly by the proposed revisions of the guidelines. First, because of the requirement that all changes in protocol have to be approved by the NIH office of recombinant DNA activities, we have often been subjected to unnecessary delays. For example, in the past it has taken as long as 1-2 months to gain approval to use a certified EK2 host-vector system which was not listed on our original memorandum of understanding and agreement. The provision requiring approval of minor changes in protocol at the national level inhibits the development of new experimental strategies within the context of existing guidelines, impedes progress and, in my opinion, does not serve the welfare of the public. By shifting more responsibility to local committees, long delays in implementing non-substantive modifications of protocols or direction could be avoided. Second, the lowering of containment requirements for shotgun experiments with adult primate DNA from P4 + EK2 to P2 + EK2 will make it possible for many laboratories to approach the question of the molecular basis of genetic disorders in man. For example, my laboratory and others have been studying the structure and chromosomal organization of human globin genes. Using recombinant DNA procedures we have isolated large segments of embryonic human genomic DNA which carry both of the δ and β globin genes in a linked complex. One of the objectives of this research is to compare the sequences within and surrounding these genes in normal individuals to those in patients suffering from genetic disorders in hemoglobin expression (thalassaemias). In order to accomplish this it is necessary to work with adult DNA samples. Under the present guidelines cloning adult human DNA can be performed only under P4 + EK2 containment, and as I

understand, there are no certified P4 facilities presently available to U.S. researchers. Under the revised guidelines it will be possible to conduct this work with P2 + EK2 containment. Thus, progress in studying the molecular basis of thalassaemia and other human genetic disorders will be promoted substantially by the proposed revision of the guidelines.

There is one containment requirement which I feel is unjustified and inconsistent. Based on the increased confidence in biological containment, vertebrate shotgun experiments have been classified P2 + EK2 without the option of performing these experiments under P3 + EK1 containment. In your comments on Section III-A-1-a (page 33060) you indicate "However, the RAC felt that in view of their increased confidence in the biological containment offered by the EK2 system, P2 + EK2 offers more containment than P3 + EK1, and that P2 + EK2 without the option of P3 + EK1 should be the containment level for certain specified classes of experiments." I agree that P2 + EK2 is more effective than P3 + EK1 containment, but I don't understand how this should then lead to the conclusion that P3 + EK1 should not be an option. Is there evidence that P3 + EK1 does not provide sufficient containment? In light of the conclusions of the Falmouth conference, the general confidence in *E. coli* K12 as a safe vector, and years of experience with P3 containment of known pathogens, I see no compelling argument for the exclusion of the P3 + EK1 option to these experiments. Moreover, the philosophy of most effective containment is not consistently followed throughout the revised guidelines. For example, the containment requirement for cloning total transforming virus or subgenomic fragments containing transforming genes (III-A-2-a-(1)-(b)-(1)-(a)) is P2 + EK2 *or* P3 + EK1. Thus, the requirement for cloning DNA known to transform human cells in culture is more flexible than the requirement for cloning total human DNA. It is my understanding that the primary concern in vertebrate shotgun experiments is the potential biohazard of cloned endogenous viruses. If this is the case, why should the requirements for cloning endogenous viruses and intact transforming viruses differ?

An important question is whether or not significant experimental advantages are conferred by the P3 + EK1 option. I can think of two. First, in most cases bacteriophage λ EK2 cloning vectors are employed to clone specific eukaryotic genes and their flanking sequences. The total size of the vector plus eukaryotic DNA is approximately 50,000 base pairs. In order to determine the nucleotide sequence of a small portion of the cloned eukaryotic DNA, for example 500-1000 base pairs it is necessary to isolate large amounts of DNA because the DNA of interest comprises only 1-2% of the total recombinant bacteriophage DNA. To circumvent this difficulty the small fragment can be subcloned onto a small plasmid using the EK2 certified host X1776. Unfortunately, very little is gained by this procedure because of difficulties in working with X1776. In my laboratory and many others the yield of DNA from a liter of X1776 is from 5-10 times less than that obtained when plasmids are grown in EK1 hosts. Thus, the advantage of EK2 containment should be weighed against the necessity of handling much larger volumes of cells and in the process compromising physical containment

The second experimental advantage of the P3 + EK1 option would be the application of "cosmid" cloning systems to vertebrate shotgun experiments. Cosmids are bacterial plasmids bearing bacteriophage λ cohesive ends. The presence of the λ cohesive ends makes it possible to clone exceedingly large fragments of DNA (45 kilobases) using bacteriophage λ in vitro packaging systems to introduce the hybrid DNA into bacterial cells. X1776 is the only EK2 host presently available and the strain is λ-resistant. It would therefore be necessary to develop, test and certify a new EK2 host before cosmids could be used to clone vertebrate DNA.

In conclusion, I urge you to reconsider your decision against the P3 + EK1 option for vertebrate shotgun experiments. There is no evidence that this containment level is unsafe and the availability of this option provides flexibility in designing experimental strategies.

Sincerely yours,

Tom Maniatis

Tom Maniatis
Assoc. Professor
of Biology

TM:jCh

Yale University *New Haven, Connecticut 06510*

SCHOOL OF MEDICINE
333 Cedar Street
Department of Human Genetics

September 6, 1978

Dr. Donald Frederickson
Director, National Institutes
of Health
Bethesda, MD 20014

Dear Dr. Frederickson:

I would just like to express my opinion that the new proposed Guidelines for Recombinant DNA Research are if anything too stringent in the requirements on the scientific community. I would think that cloning of animal DNA in SV40 could safely be reduced to P2 conditions without any realistically conceivable possibility of harm and I would hope that new Guidelines might eventually permit this. My personal opinion is that at this point any guidelines are apt to do more harm than good in terms of producing an impediment to scientific progress.

Sincerely,

Sherman M. Weissman, M.D.
Professor of Human Genetics,
Medicine, and Molecular Bio-
physics and Biochemistry

MINISTÈRE DE LA SANTÉ
ET DE
LA FAMILLE

INSTITUT NATIONAL DE LA SANTÉ
ET DE LA RECHERCHE MÉDICALE

LE DIRECTEUR GÉNÉRAL

EL

RÉPUBLIQUE FRANÇAISE

PARIS, LE 06 SEP 1978

101, RUE DE TOLBIAC
584.14 41

Monsieur FREDRICKSON
Directeur
Department of Health Education and
Welfare
Public Health Service
National Institute of Health
Bethesda
Maryland 20014

Cher Monsieur,

J'ai bien reçu votre lettre du 1er août 1978, ainsi que les nouvelles règles que vous proposez en matière de recombinants génétiques. Permettez-moi de vous en remercier très vivement.

Restant à votre disposition, je vous prie d'agréer, cher Monsieur, l'assurance de ma haute considération. et ma meilleur sentiments

Pr C. BURG.

Dear Sir,

I received your letter of Aug. 1, 1978, with the new rules that you propose for recombinant genetic matter. May I thank you very warmly.

Remaining at your disposition, I am sincerely yours, sir, and with best wishes,

Pr C. Burg

[A-87]

AMERICAN FEDERATION OF LABOR AND CONGRESS OF INDUSTRIAL ORGANIZATIONS

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815 SIXTEENTH STREET, N.W.
WASHINGTON, D.C. 20006

(202) 637-5000

September 7, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, Md. 20014

Dear Dr. Fredrickson:

We appreciate the opportunity to comment on the NIH Proposed Revised Guidelines for Recombinant DNA Research. The specific technical details, we are sure, will be addressed by many others, but we would like to comment on certain general policies and provisions of the Guidelines.

The Guidelines currently apply only to grantees of the NIH. However, the Congress is continuing to explore extending the constraints of the Guidelines to all those engaged in this line of research, and whether or not new legislation is passed in the near future, the Guidelines will undoubtedly form the technical base upon which the Occupational Safety and Health Administration, the Environmental Protection Agency and state and local public health departments will act to protect the health of laboratory and production workers, as well as the general community.

We do not believe this is an appropriate time to weaken the Guidelines. The field is a new one, and with all due respect to the many eminent scientists active in the field (not all of whom are of the same mind, by the way. See, for example, the attached article by Dr. Jonathan King), no one can say that after only a handful of years of research on a limited number of organisms we know all the questions, let alone sufficient answers to guarantee reasonable protection of the public. We most definitely do not agree with your statement on P. 33044, Federal Register, July 28, 1978, regarding a shift in the burden of proof to those who desire to protect the health of the public by restricting Recombinant DNA research. The statement borders on irresponsibility, and must be removed.

One can understand the desire of academic researchers to push their investigations to the limit of human imagination. One can also understand the desire of industrial scientists to rapidly exploit new scientific developments without the delay that may possibly result from promulgation of protective regulations. But we feel that there is ample evidence to justify application of the old adage, "better safe than sorry". Let us cite just one example from another

area. Vinyl chloride was used commercially on a massive scale, with many workers and people living near plants being exposed to the material for many years, before it was recognized that this chemical is a potent carcinogen. One hopes that routine carcinogenicity testing is more common today than it was decades ago, but the point is that increasing knowledge based in part on past mistakes should lead us not to a false sense of security, but to a greater awareness of potential problems. There is no justification for weakening containment guidelines at this time, after very limited experience in the field, except in those specific cases where it can be demonstrated that a lower level of containment would offer the same protection to the public.

We would now like to consider Section IV of the Proposed Guildelines, "Roles and Responsibilities". Of prime concern is the composition of the Institutional Biosafety Committee (IBC). The minimum requirement is for five people with "experience and expertise to assess the safety of proposed recombinant DNA research projects and any potential risks to public health or the environment" (P. 33085). This is rather vague, given the fact that the IBC is delegated enormous power to lower restrictions, inspect facilities, approve planned experiments, and generally oversee the institution's activities in this area. If these local committees are to be given such sweeping authority, they must be constituted in such a way as to assure objectivity.

We would suggest, for example, that the committee consist of seven members, with three having direct experience in disciplines relevant to recombinant DNA technology, one with experience in other areas of biological safety, one a nondoctoral person from a laboratory technical staff, and two representatives from the surrounding (non-academic) community. The latter two should have no other connection with the institution. Additional "experts" may be used as non-voting consultants.

It is of particular importance that the IBC be shielded from institutional pressures because of the authority given them to approve experiments prior to NIH review, as well as the authority to lower containment levels. The only way to do this is to assure that a majority of the committee members not have a close relationship with recombinant DNA research, and that some of the members not have any other connection at all with the institution.

The IBC is given the duty of insuring that laboratory safety standards are being followed. The results of its "periodic inspections" (P. 33085, IV-A-3-a) must be made public.

Sec. IV-A-4-o should be modified to make it a requirement that containment procedures be included in any publications, in part to discourage violation of the Guidelines through close peer review.

Violations of the Guidelines result only in "suspension, limitation, or termination of financial assistance" (P. 33087). This is insufficiently vague. NIH should establish a ranking of possible violations by possible risk to laboratory workers or the community, and set definite penalties in each case. Further, violations of the guidelines should be widely publicized by NIH.

Routine medical exams for laboratory workers should be required, as a responsibility of the principal investigator.

Reporting of possible violations must be encouraged. NIH must devise a system (perhaps through binding agreements with the institutions) for the protection of those who exercise this responsibility.

Finally, a comment on the RAC itself. It is time to end the practice of experts talking to themselves. The RAC must be broadened to include more people who are not involved with recombinant DNA research, or indeed, any microbiological research. It must also include more non-scientists and representatives of labor and the general public. This is so because the committee must deal with issues that go far beyond basic technical issues; it must be representative of the community as a whole, because the entire community is subject to the potential risks.

Dennis Chamot, Ph.D.

Sheldon Samuels

Co-Chairmen
AFL-CIO Staff Subcommittee
on Recombinant DNA Research

[Enclosed with this letter was an article by Jonathan King, Recombinant DNA and Autoimmune Disease, J. Inf. Dis., 137:663-666.]

SOLOMON GARB, M.D., F.A.C.P.
7159 SOUTH FRANKLIN WAY
LITTLETON, COLORADO 80122

September 8, 1978

Dr. Donald Fredericksen, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredericksen,

I support fully the position and statement of Friends of the Earth concerning the proposed revisions of the NIH recombinant DNA guidelines. There is no need to repeat the details. I believe that beyond the particular question of specific guidelines is the more important question of the public perception as to whether or not scientists are willing to accept public participation in matters that affect the public.

Yours truly,

Solomon Garb

Solomon Garb, M.D.

SG/gr

cc: Pam Lippe
Senator Kennedy

TUFTS UNIVERSITY

Graduate Program in Urban Social and
Environmental Policy

September 8, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

As a former member of the Cambridge Experimentation Review Board who participated in the first citizen review of its type in the history of American science on the hazards of recombinant DNA research I have some sincere concerns to express about the newly proposed guidelines for the research (Federal Register, July 28, 1978). My remarks will focus primarily on Section IV of the revised guidelines entitled "Roles and Responsibilities."

On the favorable side, I find that there are many positive additions in these revised guidelines. Many areas are spelled out in greater detail, with more clarity and with greater attention given to public accountability than I find in the original guidelines. I wish to congratulate you in producing a document that reads more easily to the informed citizen.

The concerns I wish to raise fall into the following categories: Medical Surveillance; Institutional Bio-Safety Committee; Biological Safety Officer; Recombinant DNA Molecule Advisory Committee.

1. Medical Surveillance

According to Section IV A-1-e (Fed. Register, 33084) institutions have the discretion to determine the necessity of medical surveillance. Such discretion given to institutions will result in vastly different standards. Many out of economic exigency or pressure from investigators will seek the path of least resistance. Under such provisions smaller institutions which do not possess the full range of environmental medical services are unlikely to be in a position to initiate the kind of medical surveillance procedures that larger institutions are capable of where such services are already available.

Medford, Massachusetts 02155
617 628-5000

One of the requirements of the Cambridge City Ordinance for Recombinant DNA research, responding to the many concerns about the lack of concrete data on the risks of many varieties of experiments was a strong program of medical surveillance and epidemiological monitoring.

An argument has been made for a single national standard under which recombinant DNA molecule work would be carried out in contrast to a minimum standard with additional requirements established by states or local communities. This argument is severely weakened when individual institutions are permitted considerable discretion in such areas as medical surveillance. Since the guidelines may be serving as the standard to which many private laboratories will conform, I believe it is important that medical surveillance criteria be specified in greater detail. At the minimum, for each laboratory engaged in recombinant DNA molecule work there should be a mandatory requirement that:

(1) records be kept of all agents used
(2) records be kept of all modified organisms created
(3) records be kept on all laboratory acquired illnesses (this may be covered in Sect. IV A-4-n-(3)
(4) maintenance of base line serum

The above information should be available to local public health officials.

2. Insitutional Bio-Safety Committee (IBC)
To avoid cases of conflict of interest, no member of the IBC should be an individual who is principal investigator actively engaged in recombinant DNA research. I propose this in lieu of the weaker provision (Sect. IV -A-2) No member of an IBC may be involved (except to provide information requested by the IBC) in the review or approval of a project in which he or she has been, or expects to be engaged, or has a direct financial interest.

Under Section IV -A-2-b an IBC can approve single step reductions in containment levels for certain experiments, without review and final approval of NIH. This is a worrisome provision for the following reason. The impact of having a standardized review process is lost if substantial discretionary decisions such as step-wise reductions in containment are given to local boards. Single-step reductions in containment levels from P_3 to P_2 represent a substantial reduction in safety. That such decisions will be made without the oversight and final review by NIH will reinforce a weakening of the regulatory process.

3. Biological Safety Officer
Under Section IV -A-3 a biological safety officer is required for those institutions engaged in recombinant DNA research at the P-3 or P-4 level.

Since the impetus has been to reduce the containment levels for experiments while the classification of experiment types of those levels is still a subject of considerable controversy among members of the scientific community, I propose that a biological safety officer should be designated for any institution where any recombinant DNA work is carried out.

The rationale developed by the Cambridge Experimentation Review Board is that the Principal Investigator of a recombinant DNA project be clearly distinquished in purpose and responsibilities from the bio-safety officer. This principle should hold for all levels of containment unless it is universally agreed that there is zero risk. The fact that some experiments have been classified as potentially less hazardous does not negate the importance or need for a biological safety officer.

4. Recombinant DNA Molecule Advisory Committee (RMAC)

I would like to see the RMAC include in its composition representatives from OSHA and EPA. In this way the American public will be assured that a conscious effort has been made to (1) emphasize the concerns of the laboratory worker (2) take cognizance of a broad class of environmental concerns. Representation on the RMAC from these agencies should have full status on the committee.

I want to make it clear that the afroementioned recommendations are my personal ones.

Sincerely,

Sheldon Krimsky

Sheldon Krimsky, Ph.D.
Acting Director
Program in Urban Social
and Environmental Policy

SK/lmc

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ СССР
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Рахмановский пер., д. 3.

Телефон 295-11-40
Управление внешних сношений

8 сентября 78 № 22/7-119

на №

Д-ру Дональду С.Фредриксону

Директору Национальных институтов
здравоохранения
Бетезда, Мэриленд 20014, С Ш А

Уважаемый д-р Фредриксон,

Благодарим Вас за присланные Вами материалы, касающиеся проведения научных исследований в области рекомбинантов молекул ДНК и представляющие несомненный научный интерес (Ваше письмо от I августа с.г.). Все полученные материалы будут внимательно рассмотрены советскими специалистами в данной области.

Пользуемся случаем, чтобы передать Вам наши наилучшие пожелания.

С уважением,

С.П.Буренков

Заместитель Министра
здравоохранения СССР

[Editor's note: This letter is from S.P. Burenkow, Deputy or "substitute" Minister of Health, U.S.S.R. He thanks Dr. Fredrickson for sending the materials on recombinant DNA on Aug. 1 (the date revised guidelines were distributed). He then says they will painstakingly consider them and take advantage of the opportunity to give their scientific opinion.]

779—5000

22 Kensington Drive
Manalapan, New Jersey 07726
September 10, 1978

Office of the Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

In reference to an article in the July 28, 1978 issue of the Federal Register entitled Recombinant DNA Research Proposed Guidelines, I have inclosed some subjective comments.

Superficially, the proposed revised guidelines for recombinant DNA research appear politically and economically acceptable: However, guidelines based on the assumption that E. coli K_{12} cannot inadvertently become pathogenic are, at best, unscientific (ref. to page 33160 of the Federal Register 28 July, "Cloning Viral DNA's in E. coli K_{12}). I fail to comprehend how the participants at the Falmouth meeting "were unable to envisage a sequence of events which could occur with significant probability that would allow E. coli carrying either whole DNA genome of certain viruses or subgenomic fragments of virtually any virus to lead to disease." Perhaps the following flow sheet could be of some value in designing a three pronged experiment to test such probability.

Possible Series of Events Which Could Lead to Pathogenicity of E. coli K_{12}

innocuous E. coli vector
↓
laboratory disposal unit
↓
sewage
↓
inland waterways (streams; rivers etc.)
↓
coastal waters
↓
E. coli K_{12} vector containing "viral genome or subgenomic fragments of vitually any virus" would be exposed to:
↓
human waste containing large amount of unaltered normal intestinal E. coli
↓ transference of genetic information between E. coli K_{12} and unaltered E. coli
exposure to low levels of radiation and heat from nuclear power generators (rate of mutation?)
↓
exposure to non-biodegradable heavy metals (rate of mutation?)

E. coli ingested by "bottom dwellers" (polychaete worms)
↓
polychaete worms ingested by "bottom fishes" (flounder, cod, pollack etc.)
↓
<u>Human Consumption</u>

seepage of E. coli back into coastal aquifers
↓
drinking water

Guidelines based on assumptions can promote a false sense of security within the governmental; academic and industrial sectors involved in recombinant DNA research. Though DNA recombinant research technology will continue to provide answers and solutions to perplexing scientific questions, it should not be conducted with a false sense of security, for this can only lead to undesirable consequences.

In reference to the administration of the proposed guidelines, encouraging the institutional bio-hazard committees to assume a greater portion of responsibility for the scientific work conducted is an ideal goal. But, perhaps, such local control might inhibit rather than enhance the scientific freedom of inquiry via the establishment of a scientific elitism and "research-grant favoritism".

Sincerely,

Mary Jane A. Ricciutti

Mary Jane A. Ricciutti

concerned citizen

UNIVERSITY OF WISCONSIN-MADISON

COLLEGE OF AGRICULTURAL
AND LIFE SCIENCES

Department of Biochemistry
420 Henry Mall
Madison, Wisconsin 53706 USA
Telephone: 608/262-3026/262-3040

September 11, 1978

Dr. Donald Frederickson
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Frederickson:

The University of Wisconsin Biological Safety Committee discussed the proposed revised guidelines for recombinant DNA experimentation during our last meeting and moved that I should communicate to you its feelings about these proposals. I shall try to present the consensus of the meeting, however, time limitations prevent me from checking the details of this letter with the entire committee.

(1) In general, the committee felt that the proposed revisions are a good first response to the conclusions arising from the Falmouth and Ascot meetings that recombinant DNA experimentation is not as potentially hazardous as originally perceived. We particularly welcome the exclusion of intraspecific experiments and the downgrading of other experiments.

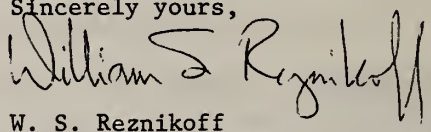
(2) Despite the obvious improvements, we are concerned that the proposed administrative procedures are excessive and disproportionate when measured against the perceived risks. We are particularly concerned in regards to our own functioning. Thus, as a result of a very worthwhile attempt to facilitate certification for the principle investigator, the local committees have been given added responsibilities. Furthermore, the administrative structure and functioning of the local committee are required to be more elaborate than necessary. Our concern about this stems from the fact that, unlike many other universities, our committee predates the recombinant DNA debate and has dealt extensively with problems arising from the handling of known pathogens and carcinogens. We have seen our recombinant DNA functions seriously erode our capability to deal with these other areas, and we feel that this is a mistake since they represent significant areas of concern. In addition, these responsibilities add an additional financial burden on our already limited resources.

(3) The Committee does not feel negative about having a non-university member associated with it; however, it feels that dictating his or her membership is a political and not a scientific or safety matter and, as such, it is an inappropriate part of safety guidelines.

(4) The term "medical surveillance" in Section IV-A-1-e is a misleading term. Perhaps "health risk surveillance" would be more appropriate.

Thank you very much for your consideration of these points.

Sincerely yours,



W. S. Reznikoff
Chairman, Subcommittee on Recombinant DNA
University of Wisconsin Safety Committee

clw

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Director, NIH
Through: ES/NIH BL

DATE: September 11, 1978

FROM : Director
Office of Recombinant DNA Activities, NIGMS

SUBJECT : Appendix A of the Proposed Revised Guidelines

At its August 2-3, 1978 meeting, the Recombinant DNA Advisory Committee unanimously recommended that in Appendix A of the Proposed Revised Guidelines, the citation "Agrobacterium tumefaciens" be changed to "Agrobacterium species" as there are only a small number of species in the genus Agrobacterium, and the species are closely related. It is the intent of the RAC that this recommendation be formally communicated to you for consideration in your review of comments on the Proposed Revised Guidelines.

William J. Gartland, Jr., Ph.D.

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DR DONALD S FREDRICKSON, DIRECTOR
NATIONAL INSTITUTES OF HEALTH
BETHESDA MD 20014

DEAR DR FREDRICKSON

THIS STATEMENT REFLECTS THE VIEWS OF THOSE ATTENDING THE WORKSHOP ON GENETIC ENGINERRING HELD ON AUGUST 31, 1978 IN ANGERS, FRANCE AT THE FOURTH INTERNATIONAL CONFERENCE ON PLANT PATHOGENIC BACTERIA. WE ARE VERY MUCH IN FAVOR OF THE CHANGES IN THE PROPOSED REVISED NIH GUIDELINES PUBLISHED ON JULY 28, 1978. THESE REVISIONS WILL MAKE IT POSSIBLE TO PURSUE MANY VALUABLE AND INTERESTING LINES OF RESEARCH ON PLANT PATHOGENIC BACTERIA THAT WE'RE HERETOFORE FORBIDDEN. WE ANTICIPATE NO DANGER ARISING FROM THE ALLOWED RECOMBINANT DNA EXPERIMENTS IN OUR DISCIPLINE.

ONE MINOR SUGGESTION WAS RAISED AT OUR WORKSHOP THAT WE SUBMIT FOR YOUR CONSIDERATION. ON THE LIST OF EXEMPTED ORGANISMS THAT EXCHANGE DNA WITH E. COLI, AGROBACTERIUM TUMEFACIENS IS LISTED BY GENUS AND SPECIES. BECAUSE THE MAJOR TAXONOMIC CRITERION FOR THE SPECIES OF THIS GENUS IS A PLASMID-BORNE TRAIT, THE DISTINCTION BETWEEN THE SEVERAL AGROBACTERIUM SPECIES IS NOT A MEANINGFUL ONE. WE SUGGEST THAT THE ORGANISM BE LISTED AS AGROBACTERIUM SPP FOR THIS REASON.

THE MAJOR POINT OF DISCUSSION AT OUR WORKSHOP WAS THE TECHNIQUE FOR GENETIC ENGINEERING EXPERIMENTS AIMED AT CROP IMPROVEMENTS. IT SEEMS CLEAR NOW THAT SUCH EXPERIMENTS ARE TECHNICALLY FEASIBLE BY USING THE AGROBACTERIUM TI PLASMID AS A VECTOR FOR INSERTION OF DESIRABLE GENETIC INFORMATION INTO DICOTYLEDONOUS PLANT CELLS. THE MAJOR OBSTACLE TO SUCH EXPERIMENTATION UNFORTUNATELY IS THE RESTRICTIONS INPOSED EVEN BY THESE REVISED NIH GUIDELINES THERE HAS BEEN NO REVISION THAT ADDRESSES THE ISSUES PRESENTED BY THESE EXPERIMENTS. THE MANIPULATIONS REQUIRED INCLUDE THE JOINING OF THE DESIRABLE DNA (PRESUMABLY PLANT DNA) TO TI PLASMID DNA IN VITRO, TRANSFORMATION OF AGROBACTERIUM TUMEFACIENS WITH SUCH AND ENGINEERED PLASMID AND TRANSFORMATION BY AGROBACTERIUM OF PLANT CELLS, SOME OF WHICH WILL ACQUIRE THE DESIRED DNA. THERE ARE IN OUR VIEW TWO POSSIBLE MEANS BY WHICH THESE EXPERIMENTS, PRESENTLY EXCLUDED BY THE GUIDELINES COULD BE BROUGHT INTO HARMONY WITH THEM:

1. LICENSING OF THE TI PLASMID AND A. TUMEFACIENS AS AN APPROVED HV1 SYSTEM FOR THE PURPOSE OF THIS TYPE OF EXPERIMENT OR
2. RECOGNITION OF THE FACT THAT THE TI PLASMID IS A NATURAL EXCHANGER WITH DICOTYLEDONOUS PLANT DNA, AND EXCLUSION FROM THE GUIDELINES OF DNA RECOMBINANTS BETWEEN THE TWO.

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IT IS OUR VIEW THAT GENTIC ENGINEERING EXPERIMENTS WITH PLANTS ARE SAFE AND FEASIBLE. WE BELIEVE THAT RESEARCH IN THIS IMPORTANT AREA SHOULD NOT BE IMPEDED. WE SEEK YOUR ASSISTANCE GUIDANCE AND COUNSEL IN CHOOSING THE BEST AVENUE BY WHICH THE GUIDELINES CAN BE BROUGHT INTO HARMONY WITH THESE LINES OF RESEARCH.

WE REITERATE OUR APPROVAL OF THE CHANGES THAT YOUR COMMITTEES HAVE ALREADY SET FORTH IN THESE REVISED GUIDELINES. OUR CONCERN ABOUT THIS ONE REMAINING PROBLEM IN NOWAY DIMINISHES OUR APPROBATION FOR THE PROGRESS ALREADY MADE.

SIGNED BY THE FOLLOWING WORKSHOP PARTICIPANTS

MARY DELL CHILTON, UNIVERSITY OF WASHINGTON, SEATTLE
JOHN D KEMP, UNIVERSITY OF WISCONSIN, MADISON
JEFF SCHELL, STATE UNIVERSITY OF GENT, BELGIUM
DON MERLO, UNIVERSITY OF MISSOURI, COLUMBIA
ANNE VIDAVER, UNIVERSITY OF NEBRASKA, LINCOLN
DAVID C SANDS, MONTANA STATE UNIVERSITY, BOZEMAN

16:33 EST

MGMCOMP MGM

TO REPLY BY MAILGRAM, SEE REVERSE SIDE FOR WESTERN UNION'S TOLL - FREE PHONE NUMBERS

UNIVERSITY OF WISCONSIN-MADISON

COLLEGE OF AGRICULTURAL
AND LIFE SCIENCES

Department of Biochemistry
420 Henry Mall
Madison, Wisconsin 53706 USA
Telephone: 608/262-3026/262-3040

September 11, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Building 1, Room 124
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

This letter is in response to your request of August 1, 1978 for comments on the Proposed Revised Guidelines on recombinant DNA research which were published in the Federal Register on Friday, July 28, 1978 (part IV).

These Revised Guidelines are a great improvement over the 1976 Guidelines. I urge you to approve them.

It is now apparent that the original Guidelines were an over-reaction and a complex bureaucracy has developed because of this. I urge you to take the necessary steps to institute the least amount of regulation on recombinant DNA research. This type of bureaucracy is counter-productive to the advancement of biomedical research in the application of scientific developments to the betterment of mankind.

Thank you.

Sincerely yours,

R. D. Wells.

Robert D. Wells
Professor of Biochemistry

RDW/zb

Baylor College of Medicine
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY • 713 790-4472
Influenza Research Center • 713 790-4469
Immunology Section • 713 790-3127

September 11, 1978

Dr. Donald S. Fredrickson
Director, National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

I wish to endorse the procedures recommended for control of recombinant DNA and related research as described in the Federal Register of July 28, 1978, beginning on page 33069 and as outlined in Table III (two sections) page 33079 and Table IV page 33083.

Respectfully yours,

Vernon Knight, M.D.
Professor and Chairman

Vk lo

[A-105]

TEXAS MEDICAL CENTER • HOUSTON, TEXAS 77030

The Joseph and Rose Kennedy
Institute of Ethics

Georgetown University
Washington, D.C. 2005

202/625-237

11 September 1978

The Honorable Joseph Califano
Secretary, D.H.E.W.
200 Independence Ave., S.W.
Room 615F
South Portal Bldg.
Washington, D.C. 20201

Dear Mr. Secretary,

Given the fact that it is almost traditional for the Secretary of H.E.W. to receive brickbats, I thought I should send a brief note with kudos. I have just finished reading the rules for recombinant D.N.A. research.

Without a doubt all sorts of people will be dissatisfied with a decimal point here and there. In toto, however, it is a first rate job which will stand science in excellent stead. A very volatile subject has been defused with prudence and common sense, without impeding the forward movement of this important work. You and your department deserve the highest praise for taking us into the modern research era of freedom of inquiry with a balancing of public interest in safety. It is a job very well done.

Sincerely yours,

Andre E. Hellegers, M.D.
Director, The Kennedy Institute of Ethics
Georgetown University

AEH/ch

THE ROCKEFELLER UNIVERSITY
1230 YORK AVENUE · NEW YORK, NEW YORK 10021

September 11, 1978

Dr. Donald Fredrickson, Director
National Institutes of Health
Bldg. 1 Rm. 124
Bethesda, MD 20014

Dear Dr. Fredrickson,

Thanks for a job well done. The Proposed Revised Guidelines for Recombinant DNA Research are in every way a success. I am especially happy to see the long awaited shift of some discretionary power from the N.I.H. to the institutional biosafety committees. Surely this arrangement will result in more efficient and studied management of the research, and should save those of us whose work falls within the scope of the Guidelines from many of the frequent and unnecessary delays that have fatigued us for the past two years.

Provision has been made for private industry to voluntarily register projects with the N.I.H. Thus the Guidelines both welcome industrial participation and test the argument that, if given the opportunity, codes of practice established by the N.I.H. will be incorporated without the threat of penalty for non-compliance. I think we will be pleasantly surprised.

Finally I would like to applaud your attempts to draw clear limits on the applicability of the Guidelines--the exemption of experiments which involve "naked" DNA and "rearranged" DNA. We finally cleared the air with regard to where justifiable safeguards end.

Sincerely,

Michael W. Young

Michael W. Young
Assistant Professor of Genetics

MWY:bc

Department of Energy
Washington, D.C. 20545

SEP 12 1978

Dr. Donald S. Fredrickson
Director, National Institutes
of Health
Bethesda, Maryland 20014

Dear Don:

We have reviewed the Proposed Revised Guidelines for Recombinant DNA Research, and we give them our strong endorsement. Also, after they have become final we would place under voluntary registration all projects we support dealing with recombinant DNA.

Sincerely,

James L. Liverman
Deputy Assistant Secretary
for Environment

ON PUBLIC PARTICIPATION:
COMMENT ON PROPOSED REVISED NIH GUIDELINES
FOR RECOMBINANT DNA RESEARCH

Dorothy Nelkin

September 12, 1978

Program on Science, Technology, and Society
628 Clark Hall, Cornell University
Ithaca, N.y. 14853 (607) 256-3810

[A-109]

ON PUBLIC PARTICIPATION: COMMENT ON PROPOSED REVISED NIH GUIDELINES FOR RECOMBINANT DNA RESEARCH

Dorothy Nelkin

I would like to comment on the proposed revised guidelines for recombinant DNA research, and in particular on the issue of public participation as outlined on page 33045 and in Part 4 of the Federal Register, July 28, 1978. Many recent controversies over science and technology suggest the growing erosion of trust in decision-making authority as citizens increasingly seek accountability, demystification, and often a more direct voice in policy decisions. The DNA dispute suggests that science itself is not exempt from such public scrutiny. This problem of trust has stimulated governmental efforts to involve citizens more directly in the creation and implementation of policies, and administrative agencies are groping for ways to make their decision-making procedures more sensitive to citizen voices and therefore more acceptable. Participation has become a sort of "catchword" for these efforts and indeed appears in the proposed revised DNA Guidelines.

Participation however is an ambiguous and often threatening concept. As a principle it is a source of legitimacy, but as a procedure it may be inefficient and obstructive. There is considerable fear that greater public involvement may virtually paralyze science and technology. Thus participatory measures are instituted with reluctance and great caution. It seems useful at this point to look critically at some of the existing participatory procedures as the N.I.H. considers participation in the form of "public notice" and the increase of "public" members in the I.B.C.

Most participatory reforms simply expand the possibility of informing the public about decisions. Other procedures channel

information from the public to the decision-making agencies, and some procedures open the administrative process to negotiation when public representatives actually share in decision-making authority.

Informing the Public

The public notice procedures, using the Federal Register, follows from the Administrative Procedures Act (1948) in which the rules and standards which form the basis of regulatory action are published in the Register prior to final adoption. The Freedom of Information Act (1966) expanded access to information about agency policies by requiring publication in the Register of decision-making procedures in general policies as well. The assumptions underlying these requirements is that in order to become involved the citizen must have access to data and reports that reveal the actual process of decision-making as well as the information on which agencies' decisions are based. Indeed the Federal Register is widely available and is scanned by citizen groups for reports that are relevant to their interests. However the Register is cumbersome, containing more than 60,000 three-columned pages per year. In addition the high cost of obtaining information under the Freedom of Information Act often discourages citizen groups. Most requests come from businesses seeking information about competitors and lawyers involved in liability suits.[1]

The National Environmental Protection Act probably provided the most significant advance in public access by requiring Environmental Impact Statements. The document must be written to solicit public opinion; drafts as well as final copies must be made available at a cost not exceeding the charge of reproducing the materials. More important, agencies are encouraged

to publicize the existence of the documents by contacting organizations with recognized environmental interests.

All these provisions for document access open possibilities for citizen intervention and give environmentalists a legal instrument to influence or delay projects. They do not, however, in themselves assure participation. For, on the working level, these procedures by themselves are limited, being entirely passive and leaving the burden on individual citizens to inform themselves. Even when agencies set up procedures to help public access, the costs of obtaining information are high: keeping up-to-date on notices in the Federal Register is time-consuming, and obtaining information may include transcript or duplication costs. There are few provisions for staff to help those who do not know exactly what documents they need. Moreover, the most crucial information may not be available at all. For example, the budget of an agency is a crucial indicator or priorities. Knowing the budget allows one to distinguish real choices from mere public statements. Detailed budget information, however, is usually hidden from public view.

While open information is curical, meaningful participation must also allow opportunities for interested groups to inform agencies about their concerns, values, and preferences.

Informing the Agency

Legislation delivers priorities and broad mandates to administrative agencies, but it is rule-making procedures that actually shape policies. Thus, the public must participate in these procedures if it is to have any real influence. Rule-making in most agencies includes requirements for public comment. However, while notice-and-comment procedures are frequently used, they tend to favor established groups who monitor

the Federal Register and who are sufficiently informed to recognize their interest in specific actions. Moreover, agencies are not bound by public comments and can ignore them.

When agencies are under pressure to encourage public input, the most frequent response is to expand the public hearing process. Public hearings may have several functions.[2] Often they simply present an opportunity to inform interested parties about proposed projects. But agencies, hoping to avoid litigation, also use public hearings to defuse anticipated conflicts, and, sometimes, to discover the ideas of participants.

In 1970, the Corps of Engineers developed an experiment to expand the public hearing process. Its' experience illustrates both the value and the limits of the hearing as a means of participation. Faced with continued controversy in the early 1970's, the Corps announced a new "open" policy to synchronize public hearings with the evolution of a particular project proposal.[3] Hearings were first held at the exploratory stage of planning to discover which issues needed consideration. Then a second set of hearings were called to evaluate public support for alternatives. A third series of hearings prior to implementation were intended to allow last-minute modifications. The Corps also held meetings with community leaders to contact the full range of interested parties. Even critical environmental groups applauded these procedures.

Despite apparent success, the Corps soon retreated from its aggressive pursuit of citizen involvement. Although the hearings had improved its public image and sparked useful dialogue, the experiment did not, as anticipated, prevent conflict. For the conflicts showed more that simple misunderstanding; they revealed a basic disagreement over the relative values of technological development and environmental conservation. Participatory mechanisms further exposed and thus intensified those disagreements.[4]

An important and unresolved issue in recent discussion about participation is the question of standing: who should be included to represent the public? Efforts to answer this question show up in debates about the "public intervenor". The right of citizen representatives to intervene as "full parties" in adjudicative hearings has been clarified and extended by recent legislation. The actual ability to intervene, however, is significantly restricted by the agencies; they determine who may participate and what issues may be contested.[5] Moreover, agencies frequently use the willingness of a group to bear the costs of intervention as one measure of commitment. Yet intervenors often lack the necessary resources to present a convincing argument. Businesses consider intervention in regulatory procedures to be a necessary investment and they can take tax deductions, or add residual costs to the price of their products.[6] The concerned citizen, however, quickly discovers the high cost of acting on his beliefs; for the purchase of scientific expertise compounds routine costs of time and travel.

Several groups have considered the idea of financing intervention.[7] But controversy surrounding these proposals (e.g. Senator Kennedy's 1976 prosed Public Participation in Government Act) suggests the general ambivalence about expanded public influence. Supporters feel that greater participation would make agencies more accountable to the public and would also educate citizens about the process of decision-making. Opponents warn of the high costs of intervention and note the difficulties of distinguishing between deserving and undeserving groups. Funding citizen intervenors, it is feared, would open agency doors to narrowly based interests, and to a flock of conflicting demands. True, it might produce greater information, but it also might create the administrative nightmare of publicly-financed opponents blocking federally supported projects.

Most participatory measures pose little challenge to the existing decision-making authority. A third set of procedures is intended to provide more substantial and collaborative forms of public participation.

Collaborative Participation

In the formal participatory procedures discussed above, government agencies still have the right and the power to disregard citizen concerns. What distinguish the more collaborative kinds of participation is the inclusion of public representatives, not simply as informants, but as partners with some power to assure that agencies act on the basis of their preferences. Collaborative procedures include the chance for participants to evaluate information and to negotiate the solution of conflicting priorities. Perhaps the most striking feature of such procedures, however, is their rarity.

Advisory boards are the most frequent form of collaboration. In 1975, forty-five government agencies had 1,267 advisory boards with a total of 22,256 members. A survey of federal agency advisory boards found that nearly 50% of the board members were industry representatives, while consumer and environmental groups comprised less than 7%.[8] Agencies justified this by claiming that citizens' groups were disinterested, lacking in technical qualifications, or simply inappropriate. The citizens' groups, however, felt that agencies avoid outside pressure by controlling the memberships on boards. Nonetheless, citizen representation on such boards is a crucial step towards a more open participatory procedure. While agencies are often not formally obliged to use the recommendations of advisory boards, arbitrary action is rare. For board membership is often representative of powerful groups, whose support may be necessary for effective policy implementation.

In lieu of effective participatory procedures citizens are increasingly taking their concerns to the courts and to the ballot box, defining participation through direct protest. Litigation has become a major channel of public involvement, especially in environmental policy. Between 1970 and 1975, there were 332 suits against federal agencies for inadequate EIS reports. Only 64 were sustained, but the threat of litigation has remained a powerful participatory tool.[9]

The referendum is a form of direct citizen participation that may effectively pre-empt administrative authority. Referenda are a prominent and increasing feature of the United States political landscape, ranging from issues such as property taxes to airport expansion or nuclear power plant development.[10] Twenty-one states have methods for placing issues on the ballot by obtaining a given number of signatures. Twenty-three states as well as hundreds of cities permit direct legislation by voting, and 38 states have some form of referenda allowing voters to review laws passed by the legislature. These procedures encourage citizens to develop legislation or to repeal existing laws.

The Problems with Participatory Reforms

Administrative agencies implement participatory mechanisms with ambivalence. On the one hand, deeply-rooted democratic values hold that the public has a "right" to information and that more direct citizen involvement will reduce conflict and improve the reasonableness of decision-making. On the other hand, the role of expertise remains central to assuring the efficiency of administrative procedures. Agencies fear that participatory measures will only encourage demands from self-appointed public representatives who lack any significant technical knowledge and who can seriously obstruct the decision-making process by costly delays and short-sighted decisions. Ambivalence is shown by procedural biases that limit implementation of participatory objectives.

One consistent feature of participation requirements is their lack of specificity. Implementation of participatory measures raises the problem of who will be involved, yet few participation requirements have comfortably dealt with this question. In this context, representation may be biased towards small, but well-organized groups with few claims to represent the "public". Without more specificity, administrative discretion prevails. It is the agencies that select members of advisory committees; the people who may speak at open committee or staff meetings; the individuals to contact when legislation calls for notification of the "people directly affected" by an action; and the individuals who have administrative standing to initiate grievance procedures. Lack of specificity allows manipulation; if agencies do not specify procedures, efforts to increase public involvement can become undermined by an uncertain, discretionary, and arbitrary environment.

The timing of public involvement further limits potential public influence. Most opportunities for participation are offered late in the decision-making process; usually citizens can only react to proposals already developed and accepted by agency staffs. Because public involvement occurs so late in the process, the burden falls on public intervenors to prove there are problems with a project (even though it is the applicant who formally bears the "burden of proof"). If the public enters the decision-making process after significant choices are already made, it can only accept or veto. Consequently, the public becomes a "nay sayer", perpetuating prejudice on both sides: government is the "enemy"; the public only plays a negative role.

Finally, the problem of cost limits effective participatory procedures. Participatory measures such as intervention have considerable potential for influencing decisions, but to effect a decision, an intervenor must be able to present a

polished, informed, and technically strong argument. Costly legal and scientific expertise is necessary to prepare and to effectively argue a case.[11] This may effectively subvert the "right" of participation.

At this time, administrative priorities of efficiency and bureaucratic autonomy cast doubts on any real commitment to participation. Participatory mechanisms are directed more towards creating public support than towards changing the balance of existing authority--more towards creating informed consent than towards expanding democratic choice. Often, the procedures detour into paperwork--hardly a reasonable substitute for genuine involvement.

However, the participatory impulse continues to place demands on administrative institutions. New mechanisms to broaden public involvement and to bring new groups into the decision-making process have multiplied. In the U.S. these have included citizen juries and various mediation techniques. In Europe, efforts to foster greater acceptance of science and technology through expanded public involvement include the Windscale public inquiry in England, the extension of the Study Circle concept in Sweden, public debates on nuclear power in Austria, reforms of local public inquiry procedures in France, and the early publication and dissemination of "policy intentions" in Holland.[12]

As governments grope for ways to meet demands for greater public involvement, genuinely difficult questions remain. Who should be involved in major policy decisions concerning science? How can those effected by policy choices be properly informed in complex ethical areas so that they can effectively and responsibly participate? Can we increase public participation without seriously obstructing important areas of scientific advance? Given the erosion of trust in our society, it is

critically important that we actively experiment with various forms of public involvement, seeking effective and workable arrangements that avoid simple cooptation. For ultimately the acceptability and support of science and technology, and the legitimacy of authorities responsible for implementing science policy may depend on finding workable and acceptable mechanisms for public participation.

FOOTNOTES

1. Nicholas Wade, "Freedom of Information Officials Thwart Public Right to Know," Science, 175, February 4, 1972, pp. 498-502.

2. Thomas Heberlein, "Some Observations of Alternative Mechanisms for Public Involvement: The Hearing, Public Opinion Poll, the Work Shop, and the Quasi-experiment," Natural Resources Journal, 16, January 1976, pp. 197-212.

3. B.H. Dodge, "Achieving Public Involvement in the Corps of Engineers Water Resources Planning," Water Spectrum Bulletin, 9, 3, June, 1973, p. 449; James Hanchey, Public Involvement in the Corps of Engineers Planning Process, Springfield, Va., National Technical Information Service, U.S. Department of Commerce, 1975.

4. Dan Mazmanian, "Participatory Democracy in a Federal Agency," Water Pollution and Public Involvement, H. Doerksen and J. Pierce (eds.), Ann Arbor Science, 1976.

5. Tersh Boasberg, "Implications of NSF Assistance to Non-profit Citizen Organizations," Washington, D.C., 1977, pp. 132-134; and Roger Cramton, "The Why, Where and How of Broadening Public Participation in the Administrative Process", Georgetown Law Journal, 60, 3, February , 1977, p. 529.

6. See Charles Goetz and Gordon Brady, "Environmental Policy Formation and the Tax Treatment of Citizen Interest Groups", Law and Contemporary Problems, 39, 4, 1975, pp. 211-231.

7. National Academy of Sciences, NRC Committee on Environmental Decision-Making, Decision-Making in the Environmental Protection Agency II, Washington D.C., 1977, pp. 102-113.

8. J. Sullivan, "Public Participation in Federal Energy Advisory Committees", draft report to the National Council for the Public Assessment of Technology, mimeo, 1976.

9. For a review and bibliography on citizen litigation, see J. DiMento, "Citizen Environmental Litigation and Administrative Process", Duke Law Journal, 22, 1977, pp. 409-52.

10. W. Bruce Shepard, "Participation in Local Policy Making: The Case of Referendum," Social Science Quarterly, 56, June 1975, pp. 55-70.

11. See Ernest Gellhorn, "Public Participation in Administrative Proceedings," The Yale Law Journal, 81, 3, January 1972, p. 367. Gellhorn states:

"Estimates of the fees charged by attorneys in 'typical' cases began at $4,000 for comparatively simple ICC tariff proceedings. Fees for formal rulemaking proceedings at the FDA are estimated, conservatively, at $4,000. Intervention in a major FTC proceeding might cost $100,000 or more in fees. Major rate proceedings in the CAB, FCC or FPC and major licensing contests in the FCC or FPC often generate fees in excess of $100,000."

12. Dorothy Nelkin, Technological Decision and Democracy, SAGE Publications, 1977.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL CANCER INSTITUTE

September 12, 1978

Dr. Donald Fredrickson
Director, NIH
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I would like to comment on the Proposed Revised Guidelines for recombinant DNA research. The proposed reduction in some of the excessive controls and restrictions on this kind of work is amply justified by all information available. These changes in the Guidelines will no doubt facilitate and accelerate the application of recombinant DNA technology to many important projects in basic and applied research without creating any hazard to workers or the general population.

I would like to urge that serious considerations be given to the possibility of further reducing regulatory levels in this area. In practice it would probably be most effective if the Proposed Guidelines were put in force while the possibility of further changes is considered. From all information available, much of which is referred to in the Proposed Guidelines, it is clear that no single documented fact has come to light that would actually show any hazard deriving from recombinant DNA or organisms harboring such DNA. Further, on the basis of existing knowledge it is very difficult to construct a logical scenario of a dangerous situation. Given these facts one must question on general grounds the need for regulation of these activities. In particular, it would seem quite clear that characterized cloned eukaryotic DNA elements in *E. coli* pose no conceivable hazard. I would like to suggest that consideration be given to a change in the Guidelines so that institutional biohazard committees would be empowered to exempt characterized clones from further regulation. Such action would be most appropriate on the basis of known facts and would reduce the regulatory burden on all parties concerned.

Sincerely yours,

Igor B. Dawid, Ph.D.
Head, Developmental Biochemistry Section
Laboratory of Biochemistry

[A-122]

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY

Shrewsbury, Massachusetts 01545

Telephone (617) 842-8921

September 12, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Department of Health, Education
and Welfare
Bethesda, Maryland 20014

Dear Don:

I am writing to you in response to the publication in the Federal Register of the new guidelines for recombinant DNA research. I find it tragic that we must continue restrictive guidelines for research of such enormous potential benefit to mankind after all evidence indicates the absence of significant risk. By doing so we seem to deny all we have learned of genetics, evolution and molecular biology in the last century. Living organisms have been recombining staggering numbers of DNA molecules for billions of years through transformation, transduction, conjugation and sex and it is the extremity of presumption to think that five years of man's experimentation can produce an unexpected pathogen. As we gain new knowledge through recombinant DNA experimentation, we find less and less justification for the imposition of regulations. We must insure that this most powerful tool of molecular biology is not fettered into impotence.

Sincerely yours,

Mahlon B. Hoagland, M.D.
President and Scientific Director

MBH:jf
cc: Dr. Wallace Rowe, Chief
Laboratory of Viral Diseases
National Institute of Allergy
and Infectious Diseases

September 12, 1978

Dr. Joseph G. Perpich
Building 1, Room 137
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Perpich:

This note is in response to your August 7, 1978, request to me for comment on the proposed revised guidelines for Recombinant DNA research.

Because the large scale industrial use of recombinant technology may pose unique risks and problems not encountered in the research laboratory, the membership should include at least one scientist from a regulatory agency, who is familiar with manufacturing processes and potential hazards. This is of particular importance since the NIH guidelines have not yet been extended to the private sector.

Rosa M. Gryder, Ph.D.
Staff Science Advisor
Office of Health Affairs/FDA

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

CENTER FOR CANCER RESEARCH

77 MASSACHUSETTS AVENUE, CAMBRIDGE, MASSACHUSETTS 02139

Room E17-539 Tel. 617/253-3013

September 12, 1978

Dr. Donald S. Fredrickson
Department of Health, Education and Welfare
Public Health Service
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

This letter is in response to your letter of August 1, 1978 soliciting comments on the Proposed Revised Guidelines for recombinant DNA research. A careful study of these documents indicates to me that they represent a very positive development in the application of recombinant DNA techniques to problems of medical relevance and should be implemented without further revision at the end of the comment period. In particular I have been seriously involved in research into thalaseemia over the past nine years. Previous NIH Guidelines have essentially made it impossible to apply recombinant DNA methodology to the understanding of this serious, prevalent and life threatening disease. I am most encouraged that the Proposed Revised Guidelines would for the first time permit application of recombinant DNA technology to this important area of research. The impact of this change is especially great if we consider thalassemia in the context of other genetic diseases such as hemophilia, Tay-Sachs disease and sickle cell anemia. Information critical to either the understanding or potential therapy for these diseases can clearly be gained through recombinant DNA techniques and I look forward with great hope to the adoption of the Proposed Revised Guidelines so that this potential may be realized.

In addition to the major benefit of opening new areas of research I believe that the Proposed Revised Guidelines rationalize the administrative structure required for recombinant DNA research which in the past has been cumbersome. These Proposed Revised Guidelines appear to deal prudently with the potential for risk associated with recombinant DNA methodology. I believe that the experience of the last several years of work in this area have made it abundantly clear that the risks associated with this work are much less significant than those projected by the most extreme critics of this technique. I support, therefore, the overall effects of the Proposed Revised Guidelines to lower the risk classification of many types of experiments.

In conclusion, I believe that the Proposed Revised Guidelines and the associated Environmental Impact Assessment represent a rather complete consideration of the issues involved and I believe that these Guidelines should be adopted without delay.

Sincerely,

David Housman

David Housman, PhD
Associate Professor of Biology

DH/srp

UNIVERSITY OF CALIFORNIA, SAN DIEGO

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PROGRAM IN SCIENCE, TECHNOLOGY
AND PUBLIC AFFAIRS

B-031
LA JOLLA, CALIFORNIA 92093

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Professor of Biological Science and Public Policy

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Professor of Political Science

STANFORD S. PENNER
Professor of Engineering Physics

ROGER R. REVELLE
Professor of Science and Public Policy

September 12, 1978

Mr. Richard Riseberg
DHEW Office of General Counsel
National Institutes of Health
Building 31, Room 2B50
Bethesda, Maryland 20014

Dear Mr. Riseberg:

I am enclosing a copy of an article in the San Diego Union of September 10 bearing on the proposed revision of the NIH DNA Guidelines.

Sincerely yours,

Clifford Grobstein

CG:aw
Enclosure

[Enclosure published in the San Diego Union, p. C-6, 9/10/78.]

COLLEGE OF MEDICINE AND DENTISTRY OF NEW JERSEY

RUTGERS MEDICAL SCHOOL
University Heights
Piscataway, New Jersey 08854

Department of Microbiology

September 12, 1978

Donald S. Frederickson, M.D.
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Frederickson:

We have reviewed the DHEW-NIH proposed revised guidelines covering recombinant DNA research. We are pleased with revisions in the new guidelines and the saltatory effect they will have on basic research in this field. The Recombinant DNA Advisory Committee has done a commendable job in integrating the concern for public safety and the complexities of the scientific issues involved into their evaluation.

In particular, we note the beneficial effect that the freedom of research in areas of recombinant DNA involving hosts that ordinarily exchange DNA will have. This freedom reflects an increasing awareness of the low level of risk involved in these types of experiments, as documented in the report. By eliminating some of the bureaucratic "red-tape" required to perform these experiments, we can expect more rapid developments in this field.

In addition, we applaud the concept of "flexibility" in containment procedures that have been introduced in the proposed guidelines. It is our hope that the risks of the types of experiments now requiring higher levels of containment will receive the same types of review and reevaluation that those at the P1 level have received, and that the NIH will revise the guidelines for these types of experiments in the near future, where appropriate.

Sincerely,

William T. McAllister, Ph.D.
Donald Quinn, M.D.
Michael J. Leibowitz, MD, PhD
Harriet Rowe, Ph.D.
William A. Hirth, Ph.D.
Raphael J. Manninen, Ph.D.

acj

NINETY-FIFTH CONGRESS

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Congress of the United States
House of Representatives
Subcommittee on Health and the Environment
of the
Committee on Interstate and Foreign Commerce
Washington, D.C. 20515

September 13, 1978

Dr. Donald Fredrickson
Director, National Institutes
of Health
Room 124, Building 1
National Institutes of Health
Bethesda, Maryland 20014

Dear Don:

I have finally had a chance to read and digest the proposed revised Guidelines for recombinant DNA research and the accompanying documents. My immediate reaction to them is that, overall, they represent a substantial improvement over the present Guidelines. You, Dr. Perpich, and the others on your staff are to be commended for a highly competent and thorough piece of work, particularly in view of the monumental dimensions of the task at hand.

Viewing the Guidelines as a set of rules which NIH has administered as regulations, it was necessary that the revisions be much more thorough in scope, more precise in its definitions of terms and give the Director much more discretion in order to give the Guidelines proper administrative flexibility. To these ends the Revised Guidelines have largely succeeded. I am left with the feeling that NIH is undergoing a continuous learning experience in how to write and administer a responsive and realistic set of guidelines - or regulations - which provide both adequate assurances to the public that the conduct of recombinant DNA research does not pose a significant risk and allow research to proceed relatively unhindered.

However, in spite of the overall merit of the revisions, there still remain - or were created by the revisions - a number of weaknesses and ambiguities. I hope that my discussion of these points in the following pages will aid NIH's learning process.

I. Scope of the Guidelines

I note that the new section I. contains considerably more substance than the 1976 Guidelines. While this is appropriate, the pending House legislation, if it should ever come to pass, will need to be amended to include I - D on prohibitions and perhaps parts of I - E on exemptions, in addition to Sections II and III as parts of the Guidelines which will be universially applicable.

The definition of recombinant DNA need not distinguish between natural and synthetic DNA's, since the general definition of DNA would include both. However, it doesn't hurt anything to make the distinction. There is a potential problem with requiring that DNA segments be joined "to DNA molecules that can replicate in a living cell". Technically, this definition excludes cases where only the recombinant molecule may have the capacity to replicate in a living cell, but where the DNA molecule(s) to which DNA segments are joined may not be able to replicate alone. This is at least a theoretical possibility which would be covered by adopting the definition of recombinant DNA in H.R. 11192.

Under I - D Prohibitions, the reference to "potent toxins" needs to be clarified somewhat. While discussions in subsequent parts of the Guidelines distinguish between polypeptide toxins, and those requiring an entire biosynthetic pathway requiring many genes, the range of species which these toxins effect is not made clear anywhere. Clearly, if all lifeforms are included, DNA from fungi which produce antibiotics would be covered. Or does this only refer to human toxins? At the Congressional briefing, Dr. Rowe said it was intended to cover all vertebrate toxins. If so, this should be so stated in the Guidelines.

Under I -D -5, I would delete the clause, "that are not known to acquire it naturally," from the prohibition concerning drug resistance genes. The "natural" acquisition of drug resistance by pathogens, in part, no doubt, a result of the indiscriminant use of antibiotics in medicine and agriculture, has created a number of serious public health problems. The primary purpose of the Guidelines is, after all, public safety. The second part of this sentence clearly limits this prohibition to cases where the control of disease agents could be compromised, which should be the sole criterion upon which this prohibition is based.

The fact that virulent strains of Pneumococcus have acquired penicillin resistance in nature hardly justifies allowing similar experiments to be performed in the laboratory, with or without recombinants.

If NIH expects to grant exceptions to the 10 liter culture limit, particularly for industrial applications, it should address now the conditions under which such exceptions will be granted and the type of safety requirements to be imposed. The containment problems connected with the use of large volume fermenters or continuous flow centrifuges are qualitatively and quantitatively different from standard laboratory equipment. While it is perhaps considered to be a problem which will not arise because private industry is not technically within the scope of the Guidelines, it would be of value if large scale containment were considered both to put NIH on record as being concerned about industrial problems and to make it more difficult for industry to ignore the Guidelines on the grounds that their special problems have not been addressed by NIH. NIH should remain as the primary source of technical expertise on the safety of recombinant DNA activities for both the public and private sectors. Further, if legislation is passed, it will be necessary that parts II and II of the Guidelines deal with the safety of large scale and production processes as well as research laboratory procedures.

My concern with the section on exemptions is that the regulatory standard of "no significant risk" is not applied to all exemptions. In drafting legislation designed to ensure public and environmental safety, this was considered to be the only rational grounds upon which total exemptions should be based. It is possible to argue convincingly that the criteria of I - E-1, I - E-2, and I - E-3, do indeed satisfy this criterion (except for the obvious cases where the host cell or vector may already be a dangerous pathogen and would be treated accordingly). I am, however, concerned by both the lack of precision of the terminology in I - E-4 ("exchange DNA by known physiological processes") and by the fact that no safety standard is applied. Clearly, there are many cases where it could be effectively argued that recombinants between natural exchangers do indeed pose no significant risk. But, in the general case, this is not a universal truth. Specifically what is meant by "known"? Does this mean that any exchange event observed once under forced laboratory conditions is, therefore, "known", entitling recombinants made from the appropriate sources to be exempted from the Guidelines? Or does the term imply "nautral"? That is must the event be something which occurs readily in nature?

Also, ther term "physiological process" must be more explicitly defined.

In order to agrue that recombinants between "known" exchangers also pose "no significant risk", one would have to argue that on both qualitative grounds - that is, the nature of the exchange - and quantitative grounds - the frequency with which the exchange occurs in nature - that the conduct of a laboratory experiment constructing or using such a recombinant does not add to the risk already present.

In cases where the risk is intrinsically negligible, exemptions could be made under I - E-5, regardless of the degree of novelty. However, in cases where a non-novel, or natural, exchange event does result in the creation of an organism which may pose a known hazard (e.g. the transfer of plasmids containing antibiotic resistance or virulence factors to knownpathogens), the criterion of non-novelty is not sufficient for an exemption, at least not without a careful assessment of the frequency of such natural exchanges and the relative degree of hazard already present.

A few will argue that if some exchange event was ever observed even once in the laboratory, then it must have occurred countless times in nature and, the argument goes, the worst has already happened. To that I would respond that, indeed, microbial evolution is a continuing process, and that many or most of the known pathogens may well have arisen by natural exchange process, and that new ones will continue to arise. Non-novelty, per-se, is not equivalent to freedom from risk or even acceptable risk.

Therefore, I would recommend that the standard of "no significant risk" be applied to all exemptions, or, at a minimum, that the added standard of "no significant increase in risk over that present in nature" be added to I - E -4. In practice, I think you will find that such a change would have no effect upon the current list of exchangers to be exempted, and would simply tighten the criteria for granting future exemptions. Bear in mind that the foregoing paragraphs argue only against a total exemption from the Guidelines soley on the basis or whether or not a recombinantion event may have occured by a "known physiological process."

II. Containment

This section is very well done and a considerable improvement over the 1976 Guidelines. I would hope, however, that one of the next tasks of the RAC be to consider physical containment requirements for large scale and industrial procedures, for the reasons discussed under my comments on part I.

Under section II-D-2 on the certification of the Host-Vector Systems, I would suggest an expansion of section II-D-2-b-1, specifically a requirement for a thorough discussion of the physiological properties of the organism, particularly those related to its reproduction and survival and the mechanisms by which it exchanges genetic information, not simply the range of organisms with which it exchanges. For example, the ability to form spores has a direct bearing on the survival of an organism in nature. Data on such properties as whether such organisms exchange genetic material by "normal" transformation (e.g. *B. subtilis*, *H. influenzae*), transducing phages, conjugation, etc. and the degree to which each occurs in the organism's natural environment should also be required.

Section II-D-1 is a bit vague on just what criteria will be applied to the certification of non *E. coli* host vector systems. The term "comparable in containment to *E. coli* K-12" might be a little too general, particularly when the putative *host vector* system contains properties not directly comparable to those of *E. coli* or normally inhabits a rather different type of environment. *E. coli* is not a spore former, for example. Therfore, a deletion mutation in one of the genes controlling spore formation would be an appropriate requirement for approval of a spore former as an HV-1 system.

III. Containment Guidelines for Covered Experiments

In general, the reductions in containment levels specified in this section, together with the exemptions accorded to clearly safe host-vector systems, appear to be entirely justified. There still remain some ambiguities which need clarification.

Section III-A-3 uses the terms "purified" and "free of harmful genes" as criteria which an Institutional Biosafety Committee must consider in order to approve lowering containment

one level below shotgun experiment containment. However, none of these terms are defined precisely enough to guarantee any uniformity among decisions rendered by different IBC's. This section should be expanded to include more specific guidance to IBC's including criteria for purity (other than simply "99%"), what "free from"really means and how it is to be determined, and, probably most important, a definition of "harmful gene". Footnote 3 clarifies these terms somewhat, but not enough, in my opinion, to really provide adequate guidance to IBC's. The interpretation of "harmful gene" may be a bit too narrow as it is used here, in that genes which might not be harmful when expressed in their original organism could indeed be "harmful" if expressed out of context in an unrelated organism. That is, the term should be interpreted more broadly than to be limited to toxins or purely pathogenic effects. It is also essential that possible harmful effects on organisms other than man or to specific ecosystems be taken into account in making such judgements.

The assumption that risk somehow increases as the cloned DNA source is phylogenetically closer to man has been made since the earliest versions of the Guidelines were written. I still am unconvinced that it is justified, except perhaps regarding the risk of the cloned DNA harboring viral sequences which may be able to enter and propogate in human cells. Even if the cloned DNA were highly homologous to human DNA, how is it envisioned that when carried in a bacterial host, it would somehow be more dangerous to man than non-homologous DNA? Clearly, genetic modifications which might render a bacterial host more pathogenic will have nothing to do with the degree of homology DNA inserts bear to human DNA.

The argument that certain gene products might be more harmful to man if similar to human gene products might, in a few cases, have merit, but, in general, even this assumption is tenuous. Even if a bacterium produced an active human polypeptide hormone, it would somehow have to enter the blood stream to be effective. Possible risk due to the production of pharmacologically active agents will clearly not depend upon evolutionary similarity to man. In fact, such products are more likely to be specified by plant genes, or by genes from insects, lower animals or microorganisms.

My other concern with the phylogenetic argument is that potential risks to life forms other than man need to be considered as well. By being overly preoccupied with possible direct harm to humans, we may not give enough attention to potential hazards to plants, animals and microorganisms,

which, indirectly could affect humans in ways far more serious than direct effects on humans.

IV. Roles and Responsibilities

The delegation of administrative responsibility to the IBC's is, as you know, a concept which is stressed in the proposed House Recombinant DNA bill and the accompanying report. I strongly endorse revisions in the Guidelines which accomplish this. However, in doing so, one must be very careful that in the process of redefining the respective roles of NIH, the institution and the IBC's, that one does not create new administrative problems.

The revised Guidelines apportion responsibility for project approval, inspection of laboratories, decisions on individual host-vector systems or containment levels, and registration in a way which, under ideal circumstances, should work extremely well. My primary concern over this section as revised is whether or not the oversight role which must be played by NIH will be adequate to keep things from becoming too non-ideal.

I have already mentioned that the discretionary powers granted to the IBC's under IV-A-2-b to lower containment by one level for experiments with purified DNA and characterized clones should be exercised according to criteria much more specific than that outlined in section III. Otherwise, considerable non-uniformity might be expected in the decisions made by different IBC's. For the same reason, the description of the IBC's duties under IV-A-2-a should also be more detailed. The requirement for the "review and approval of facilities, procedures, practices, and the training and expertise of recombinant DNA personnel" is rather generally stated and may mean different things to different IBC's.

Does this imply that the IBC maintain constant scrutiny over the principal investigator to make sure that he or she is always in compliance with the long list of duties set forth in IV-A-4? Of particular concern is who bears the responsibility for making sure that personnel are trained in safety practices and techniques? The principal investigator is given that responsibility for those under his or her direction. But who sees to it that the principal investigator is adequately competent in using and teaching such techniques? The IBC? Does the IBC bear the primary responsibility for ensuring adequate training? Again, I fear that the wording is so general, that a whole spectrum of standards may be applied by different IBC's.

Other problems are created by so greatly expanding the duties and responsibilities of the IBC's. For one thing institutional costs will necessarily be much greater. I question whether or not grant overhead funds will realistically cover this increase as well as the other institutional costs which already are supposed to be covered by overhead.

An important unanswered question is what sort of oversight role NIH will play in guaranteeing that individual IBC's are performing according to the intent of the Guidelines. Section IV-B-1-f is much too generally stated. The registration of projects and ORDA's review of MUA's may not be sufficient to determine whether or not an IBC is functioning properly, particularly since they are not submitted or reviewed prior to the beginning of a project. The current figure of a 10 - 15% rate of disapproval of MUA's on non-trivial grounds would suggest that current IBC's are indeed not perfect. And even, if no problems exist with MUA's, is it likely that ORDA would ever find out that an IBC was not enforcing training in safety practices and techniques?

My perception of current IBC's is that they range from very competent, thorough committees which take their duties seriously, to those thrown together for the sole purpose of having something to satisfy NIH and sign off on MUA's, while generally regarding the Guidelines with contempt. While the revised Guidelines represent a more realistic response to presumed risk than the old ones, can we really expect more uniformity in the quality of IBC's?

The new requirements on the membership of IBC's are a good addition. I would suggest that NIH <u>require</u> that all IBC meetings be open (except when discussing information protected by law), and that the IBC be required to respond to any reasonable requests for information concerning institutional recombinant DNA projects.

Concerning the membership of the RAC, which has been evolving in the right direction, I would add at least one member knowledgeable in large scale and mass production processes connected with industrial fermentations.

<u>General Considerations</u>

Except for the specific points which I raised, and the sections which I think need to be made more explicit, my principal overall concern with the revised Guidelines is not one of intent, or of content. In these respects the revised Guidelines represent a highly commendable document.

What does bother me is how well they will be implemented in the real world, and whether the internal checks and balances are truly adequate.

I have said little thus far about either the Decision of the Director, or the Environmental Impact Assessment. The primary value of the latter is that it provides a discussion and justification for lowering containment levels which is genrally adequate and upon which I need not comment further. The decision statement is thorough and fairly treats the numerous points raised both in comments on the RAC proposed revisions and at the December, 1977 meeting. Those instances where I would disagree with you are covered in my comments on the revisions.

There is only one argument which you used in your discussions of the current assessment of risk which I was disappointed to see included and which I would prefer to see omitted, particularly since it does nothing logically to strengthen your arguments for lowering certain containment levels. That is the observation repeated in at least three places, that no untoward event has been observed in five years of experiments with recombinant DNA. There are plenty of valid grounds upon which to justify the lowering of containment levels without resorting to a nearly irrelevant statement from which the inference the reader is presumed to make is that somehow this proves, or at least strongly suggests, that recombinant DNA activities, in general, are without risk. All it proves is that with the systems used, the risk is not great. But, then even the severest critics did not predict a high risk. Given that most of our experience has been with E. coli systems which most would regard as posing little liklihood of risk, and that even the worst hypothetical scenarios that one could imagine still involve the occurrence of a rare event or sequence of events, five years experience and even tens of thousands of safely performed individual experiments allow one very little basis upon which to predict the occurrence of future rare events. Moreover, if one considers the possibility of long latency period diseases (e.g. cancer) as a potential hazard, then a five year time point is of no value whatsoever. While I do not wish to suggest that recombinant DNA activities pose risks comparable to exposure to radiation or chemical carcinogens, one should bear in mind that it took considerably more than five years of living with these agents to learn that they posed a considerable hazard. Therefore, even if such observations may be reassuring to some, from a purely logical point of view, they have no place in evaluating risk.

Please keep in mind that the foregoing pages address those areas of the revised Guidelines which I believe require further attention, rather than the numerous sections which are superbly done. I hope that you will find my comments helpful.

Sincerely yours,

Burke

BURKE K. ZIMMERMAN, Ph.D.
Professional Staff
Subcommittee on
Health and the Environment

BKZ:jlm

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

TO : Director, NIH

DATE: September 13, 1978

FROM : Chief, Laboratory of Biochemistry, DCBD, NCI

SUBJECT: Proposed Revised Guidelines for Recombinant DNA Research

1. I want to add one comment to my previous memo (August 18th, 1978) concerning the Guidelines revisions.

2. We now have evidence that the avian vitellogenin gene contains large intervening (nonstructural) sequences within it, providing yet another example of a gene in a higher eukaryote that cannot be properly expressed within a bacterial cell. Although there are still rather few genes that have been shown to code for RNA requiring processing that the bacterial cell is not capable of carrying out, no exception has yet been found. I am forming the very strong impression that the consistency of the finding of intervening sequences is a reflection of the universal presence of such sequences in the genes of higher eukaryotes. For this reason, I see no reason to require the EK2 level of biological containment for shotgun experiments with avian DNA.

Robert Goldberger, MD

Robert Goldberger, M.D.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

September 13, 1978

NATIONAL INSTITUTE OF
ENVIRONMENTAL HEALTH SCIENCES
P.O. BOX 12233
RESEARCH TRIANGLE PARK, N.C. 27709

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20016

Dear Dr. Fredrickson:

I have received a copy of the Proposed Revised Guidelines for Recombinant DNA Research (Federal Register 43, 33042-33178). While I am in agreement with almost all the RAC proposed revisions and their reasons for them, I would like to question the following:

The proposed containment for shotgun recombinant DNA work on non-primate mammals and birds is P2 + EK2, yet for cold-blooded animals, plants and many of the RNA and DNA viruses it is P2 + EK2 or P3 + EK1. Is there a sound scientific basis for not also allowing non-primate and bird recombinant DNA work to be also carried out under P3 + EK1? The restriction to the use of only P2 + EK2 is not a trivial point, since many experiments using EK2 vectors are extremely difficult, indeed some simply impossible (e.g., those involving lysogenic λ systems) in an EK2 system. In particular, I find it difficult to see why segments of some transforming viruses may be cloned under P3 + EK1 conditions, yet DNA from a non-primate mammal or bird in which any one sequence is diluted out at least one in 10^5 with the other sequences present cannot be carried out under these same conditions.

I would appreciate it if you could bring to the attention of the Advisory Committee this suggestion, i.e., allowing non-primate and bird shotgun DNA experiments at P2 + EK2 or P3 + EK1 levels.

Yours sincerely,

Stephen E. Harris

Stephen E. Harris, Ph.D.
Senior Staff Fellow
Laboratory of Environmental Toxicology

STANFORD UNIVERSITY
STANFORD, CALIFORNIA 94305

DEPARTMENT OF BIOLOGICAL SCIENCES

September 13, 1978

Dr. Donald Fredrickson
Director, National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

On September 12, 1978, the Working Group on Prokaryote Host-Vectors Other Than E. coli K-12 of the Recombinant Advisory Committee met at Stanford. John Spizizen is preparing a full report of our recommendations to be submitted to RAC. However, one of our recommendations can be effected by making a small change in the wording of the Proposed Revised Guidelines. As this is a minor modification that clarifies the intent of the Proposed Revised Guidelines, we recommend its inclusion at this time.

Proposal:

Section I-E-3 of the Proposed Revised Guidelines should be amended to read as follows:

I-E-3. Those that consist entirely of DNA from a prokaryotic host, including its indigenous plasmids or viruses, when propagated only in that host (or closely related strain of the same species) or which have been transferred to another host by known physiological means; also those that consist entirely of DNA from a eukaryotic host, including its chloroplasts, mitochondria, or plasmids (but excluding viruses), when propagated only in that host (or a closely related strain of the same species).

Justification:

Addition of the proposed clause will exempt the following type of experiment: An E. coli strain is constructed in which a chromosomal gene of E. coli has been enzymatically joined to plasmid DNA; this plasmid is then transferred by conjugation into another bacterial host that is not on the Director's List of bacteria that exchange with E. coli.

It seems logical that this experiment should be exempt, because it involves natural genetic exchange between two organisms both of which are exempt. The E. coli donor is exempt because it represents a gene combination that could easily arise by natural means. As the transfer can also occur naturally, the same statement applies also to the second host carrying the plasmid.

If unidirectional plasmid transfer had been accepted as an adequate criterion for inclusion on the Director's List, the strain would be automatically exempt. The reason for not accepting that criterion was that some doubts had been expressed as to whether unidirectional plasmid transfer automatically implied bidirectional transfer of chromosomal genes. However, in the present case, the ability to construct the desired recombinant is de facto evidence that it could arise by natural means.

A specific proposal was submitted to RAC by Dr. A. D. Kaiser (Stanford Medical School) in which he proposed to splice an E. coli suppressor into an E. coli transposon, then move the resulting combination into Myxococcus by P1 transduction. This strategy will allow the isolation of suppressible mutants of myxococcus and its phages, which will greatly expedite genetic studies of development and motility in that organism.

Sincerely yours,

Allan Campbell
Professor of Biology

AC/an

cc: John Spizizen
Julian Davies
Martin Dworkin
David Dubnau
Stanley Barban
Jane Setlow

Department of Biochemistry
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StonyBrook

September 14, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Md. 20014

Dear Dr. Fredrickson:

I favor the proposed revisions to the NIH Guidelines on Recombinant DNA Research. I believe that the proposed changes provide for more than adequate safeguards. At the same time, these safeguards are not so restrictive that they significantly hinder research progress or interfere with the direct application of new information and technology to problems affecting our society.

My reasons for favoring the revised Guidelines can best be illustrated by considering the changes in containment proposed for recombinant DNA studies on primates. My own work involves primate species and so I have been especially interested in this aspect of the revisions. The Guidelines now in existence state that P4+EK2 (or P3+EK3) containment must be used when constructing a "library" of recombinant DNA molecules encompassing the whole of the genetic material of a primate species. In cases where uncontaminated embryonic tissue or germ cell lines can be used as a DNA source P3+EK2 containment is allowed. These rather restrictive containment conditions were mainly a result of concern that a cryptic virus genome present in the primate tissue used as the source of DNA could be accidentally cloned.

In the Revised Guidelines, recombinant DNA experiments involving primates would require P2-EK2 containment regardless of the source of DNA. I believe these levels of containment are adequate. This belief is based on new assessments of the risk of hazard to individuals and the environment.

The consensus of scientists at the Ascot workshop about the risk of cloning viral genomes or genome fragments provide justification for lowering the primate containment levels. The virologists who attended this meeting concluded that the risk inherent in viral cloning experiments using E.coli K-12 were no more dangerous than working with the virus or nucleic acid itself. Thus cloning experiments using primate DNA do not pose any additional hazard over that associated with the actual handling of the primate tissue or DNA itself.

The conclusion of the Falmouth workshop that E.coli K-12 could not be converted into an epidemic pathogen by laboratory manipulations with DNA inserts, indicates that biological containment using the appropriate E.coli K-12 host vector combination is a significantly greater barrier to individual or environmental

contamination than previously believed. This conclusion provides strong support for lowering the levels of containment required not only for work on primates but in other situations as well.

In conclusion, the adoption of these new guidelines coupled with a continuing program of risk assessment will make possible the rapid advancement of scientific knowledge under containment conditions consistent with possible risk.

Sincerely,

Norman Arnheim
Associate Professor of Biochemistry

NA/bd

STANFORD UNIVERSITY, STANFORD, CALIFORNIA 94305
DEPARTMENT OF BIOLOGICAL SCIENCES

CHARLES YANOFSKY
MORRIS HERZSTEIN PROFESSOR
OF BIOLOGY

September 14, 1978

Donald S. Fredrickson, M.D.
Director
Department of Health, Education,
and Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I would like to respond to your letter of August 1, requesting my comments on the Proposed Revised Guidelines for recombinant DNA research.

I thoroughly approve of the changes incorporated in the revised guidelines, particularly the exemption of studies with certain organisms, the reduction in required physical and biological containment, and the changes in MUA review procedures which will eliminate the excessive and unnecessary delays in project approval which everyone is experiencing under the existing guidelines.

I personally am now convinced that there is no identifiable or foreseeable hazard associated with recombinant DNA research and therefore I feel that binding guidelines are unnecessary and unwarranted. However, I approve of the revised guidelines as a cautious interim step in dealing with this area of concern.

Respectfully yours,

Charles Yanofsky

CY/an

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September 14, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I am writing in response to the statement by Joseph A. Califano in the Federal Register regarding Recombinant DNA Research proposed revised guidelines. My letter is in behalf of this campus of Indiana University and has been prepared in cooperation with the Assistant Dean for Research, Indiana University School of Medicine.

The following is an abstract of a statement by Dr. William D. Sawyer, Chairman and Professor of Microbiology and Immunology, Indiana University School of Medicine, prepared to assist in our response. It summarizes the sentiments of our faculty concerned about future recombinant DNA research.

> ". . .the proposed revision is consistent with current knowledge (and lack thereof) and conservative. The proposed revision should, however, hasten safe exploitation of a valuable technology for the well being of mankind. I urge, therefore, that the School of Medicine support issuance by the Secretary of the Revised Guidelines.
>
> Parenthetically, my principal concern about the proposed revision relates to the issue of expression of eukaryotic DNA in prokaryotic cells. I concur that expression of RNA transcripts from eukaryotic DNA will likely be nil or minimal because the prokaryotes lack the enzymes to accomplish the processing of the transcript to permit translation. However, eukaryotic messenger RNA (mRNA; already processed in the eukaryote) can serve as template for complementary DNA (cDNA). If the latter is inserted into a prokaryote and transcribed, the resultant mRNA should be subject to translation without further processing. I believe, therefore, that distinction should be made between eukaryote DNA and cDNA formed from functional eukaryote mRNA."

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I urge you to incorporate our concern into the revised guidelines and thank you for this opportunity to contribute to the revision.

Very truly yours,

Wendell F. McBurney
Acting Dean

WFM:ga

cc: Steven C. Beering, M.D., Dean,
Indiana University School of Medicine
W. Dean Fraser, Ph.D., Chairman,
Indiana University Biohazards Committee
Glenn W. Irwin, Jr., M.D., Vice President
Indiana University-Indianapolis
Suzanne B. Knoebel, M.D., Assistant Dean for
Research, Indiana University School of Medicine
William D. Sawyer, M.D., Chairman and Professor,
Department of Microbiology and Immunology,
Indiana University School of Medicine
Eugene D. Weinberg, Ph.D., Associate Dean,
Research and Development, Indiana University-
Bloomington

EMBO EUROPEAN MOLECULAR BIOLOGY ORGANIZATION

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Dr. D. S. Fredrickson
Dept. of Health, Education, and Welfare
Public Health Service
NIH
Bethesda, Md. 20014
U S A

14 September 1978

Dear Don,

Thank you for your kind letter of September 5th. EMBO is grateful to have been given the opportunity of assisting in the development of the revised guidelines, and we hope that they can be formally adopted without significant change. They will greatly reduce the impediments to research without sacrificing levels of containment adequate to protect the environment from conjectural hazards. The decision to adopt the revised guidelines will, of course, have considerable repercussions in Europe, especially in those countries which either use the NIH guidelines or have national guidelines closely modelled on the latter.

There is one general point I would like to make which relates not so much to the revised guidelines themselves but to decisions that will have to be taken once they come into force. It seems to me that three general sorts of evidence have led to the conclusion that it is reasonable to relax the guidelines: first, there is the general argument that organisms carrying foreign DNA are likely to be at a selective disadvantage to their wild type counterparts; secondly, there is the point that the split gene organisation in eukaryotes reduces the probability of an eukaryotic gene being expressed in a prokaryote unless elaborate measures are taken to induce expression; thirdly, and perhaps most importantly, so long as E.coli K12 systems are being used there seems to be no significant risk of harm to anyone or anything. However, this confidence in the safety of E.coli K12 systems should not blind us to the fact that we are very ignorant of the ecologies and biologies of other species which might be used as host/vector systems. We must be very careful when, bolstered by this confidence in E.coli K12 systems, we try to extrapolate to B. subtilis, yeast, etc. etc.

I believe that for an organism to be classified as an HV-1 host, let alone HV-2, it should differ from the wild type by a margin comparable to the difference between E.coli K12 and a wild type E.coli, and that is a large margin. To take as a specific example B.subtilis, I believe that any strain which is capable of sporulation should not be considered as an HV-1 host. In Europe, and also in the USA I understand, some wish to propose that certain B.subtilis strains which retain the ability to sporulate should be nevertheless classified as HV-1 hosts. In my opinion that would be a travesty. Since the efficacy of biological containment is one of the chief arguments for relaxing the guidelines, surely it would be intellectually dishonest as well as politically inept to lower the criteria of biological containment when other hosts than those derived from E.coli K12 are considered.

I hasten to add that these are my personal opinions, and I apologize if this letter sounds like preaching but this question has already arisen in the EMBO Committee, where it was left unresolved, and marginally at a COGENE meeting.

With my best regards,

Yours sincerely,

John Tooze

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September 14, 1978

Mr. Richard Riseberg
DHEW Office of General Counsel
National Institutes of Health
Building 31, Room 2B50
Bethesda, Maryland 20014

RE: Exemption of the bacterium Caulobacter crescentus from the recombinant DNA guidelines

Dear Sir:

Dr. Bert Ely recently sent me a preprint of his manuscript entitled "Transfer of drug resistance factors to the dimorphic bacterium Caulobacter crescentus" and requested that I comment on the data presented.

I find the material entirely suitable for publication and except for very minor changes, mostly in grammar and typing, I would recommend its immediate submission and publication. In addition, I have independently confirmed several of Dr. Ely's observations regarding RP4 transfer and the phage sensitivities associated with RP4.

I therefore submit that it has been shown that Caulobacter crescentus freely exchanges conjugative plasmids with other bacteria including Escherichia coli, that non-conjugative plasmids can be readily mobilized by other plasmids like RP4 between C. crescentus and E. coli, and that plasmids like RP4 result in chromosomal mobilization within C. crescentus. Jollick (J. Gen. Microbiol. 99:325) has observed that RP1 will elicit chromosomal mobilization between different species of Caulobacter but that most of the exconjugants are unstable and stable recombination seems rare. These observations taken together suggest that P type plasmids mobilize C. crescentus chromosomal DNA into other organisms as well, though this remains to be demonstrated.

It is my hope that these observations will allow C. crescentus to be classified within the group of organisms known to exchange genetic material with E. coli.

Sincerely yours,

Robert A. Bender

Robert A. Bender
Assistant Professor

dm

cc: Bert Ely

[A-149]

DEPARTMENT OF BOTANY – DEPARTMENT OF CELLULAR AND MOLECULAR BIOLOGY
DEPARTMENT OF ECOLOGY AND EVOLUTIONARY BIOLOGY – DEPARTMENT OF EXPERIMENTAL BIOLOGY

THE UNIVERSITY OF ROCHESTER
MEDICAL CENTER
SCHOOL OF MEDICINE AND DENTISTRY · SCHOOL OF NURSING
STRONG MEMORIAL HOSPITAL

601 ELMWOOD AVENUE
ROCHESTER, NEW YORK 14642
AREA CODE 716

DEPARTMENT OF MICROBIOLOGY
Frank E. Young, M.D., Ph.D.
Professor and Chairman
275-3407

September 14, 1978

Dr. Donald S. Fredrickson
National Institutes of Health
Immediate Office of the Director
Building 1; Room 124
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I wish to compliment you, your staff at NIH, and the recombinant DNA Advisory Committee for the excellent job that you did on the proposed revised guidelines which were published Friday, July 28, 1978. This detailed analysis represents a great deal of work and I'm sure no small effort on your own part. I am in essential agreement with most of the revisions but I wish to raise a few additional points for your consideration and evaluation.

1.) I'm in wholehearted agreement with your prohibition of mouth pipeting in recombinant DNA laboratories. This is an important advance and should be applied to all levels of research.

2.) I concur with your exemptions 2, 3 and 4 but have some reservation in regards to the first exemption. There are not any data to my knowledge that deal with the inactivation of DNA in nature that has been thoroughly reviewed and critiqued. For instance, does closed circular DNA inactivate at a different rate than double stranded or single stranded DNA? Is the rate of inactivation different depending on what the DNA is bound to, for example soil versus laboratory surfaces? Could the DNA bind to the surface of a microbe and be released in the form of a passenger? Without these questions answered it may be less prudent to exempt inactivation of DNA at this time. The inactivation of DNA is relatively simple and it might be prudent to preserve such a precaution.

3.) I wholeheartedly support the definition of recombinant DNA research and the provisions for physical containment. I only wonder whether more specific guidelines should be developed regarding the accessibility of the autoclave in the P-2 facility. If the building is large it may not be sufficient to merely have an autoclave for sterilization of waste within the same building, particularly if one has to use stairs or elevators to find the autoclave. You may also wish to reevaluate the discretionary use of laboratory gowns within the laboratory. It seems less prudent to not wear laboratory coats in a microbiology laboratory.

4.) In general I support your concept of biological containment. It may be helpful to provide a clear assessment of the efficacy of biological containment in view of its great implementation. Although it is asthenic and nice in laboratory terms it is not clear whether this type of containment is really effective or whether K12 would be sufficiently inactivated in the environment. Thus, as Chairman of our Biohazard Committee I would particularly appreciate a critique of the efficacy of biological containment.

5.) Because the State of New York and possibly other states will be enacting legislation it is important to look at the guidelines from a standpoint of their implementation as law. I am enclosing for your reference a copy of the New York State bill. You will note that there are requirements for compliance with the NIH guidelines, registration of projects and responsibilities for education. In order to effect this compliance with maximal efficiency it will be important to have a high degree of responsiveness by the Recombinant DNA Committee. I applaud the increased delegation to the Institutional Biosafety Committee and in fact raised this strongly in my testimony at Rogers subcommittee a few years ago. Because of this increased responsibility on the part of the local biosafety committee it is imperative that NIH notify the chairman of the biosafety committee as well as "the institution" during its official feedback. It was mentioned repeatedly that NIH would notify the institutions, however it was not clarified that the Chairman of the Biosafety Committee would be notified. In order to have this individual fully informed, such notification is imperative in my opinion. It will also be imperative to have NIH provide a statement that it has certified the institution and finds that it is in compliance rather than merely noting this on the bottom of an NIH grant. Such documentation would be most helpful for the University. This is particularly important if liabilities are to accrue to the institution. While it is clear that NIH has no intention of instituting fines or other penalties beyond the grant process, state regulations may not follow the same route.

6.) It is important to give careful consideration to the registration of students who are involved in recombinant DNA projects. It would be most helpful if all of the students could be listed regardless of NIH training grant support. This would enable one central listing to serve for whatever training grant or research grant the student is supported on. I've enclosed for your reference in this matter, the information that I received from NIH in regards to my query on training grants. Possibly some of this ought to be incorporated into the guidelines.

7.) The section on a rodent and insect control is vague. I wish that this would be spelled out more clearly so that I would know as an Institutional Biosafety Committee Chairman how to access this. Possibly this will be forthcoming in some of the other appendices and amplified in these guidelines.

8.) I believe that it is imprudent to publish the list of exchanges just with the emphasis on the E. coli model system. I have two objections to this: First there is insufficient documentation and review of this contention in the literature. While I am trying to do this myself for a review to be submitted to the Annual Review of Microbiology, I believe

that it is a bit premature to jump to this conclusion at the present time. In addition to mere exchange, the possibility for exchange and the natural occurrence of exchange should be examined. It is also questionable why one should list Escherichia coli exchanges and not others in nature such as the organisms that exchange with Bacillus subtilis, with Haemophilis influenzae, with Neisseria gonorrhoeae, etc. I would therefore advise refraining publishing any list of exchanges until it is complete. This will only detract from the urgency to get the other exchanges documented as well.

9.) The Ascot Conference and the ASM committee reviewing the decrease in the level of physical containment for viruses did not have the benefit of Dr. Rowe's recent experiments that were designed to test the capacity of Escherichia coli to produce polyoma proteins. Before including the reduction in containment levels for viruses I would urge that a careful consideration be given to the recent results of Dr. Rowe's experiment so that we can have the benefit of his work.

10.) I, as well as others will be developing alternate host factor systems. It would be very helpful to have the exercise performed for us for E. coli K12 even though this is certified as an HV system. To my knowledge this has never been done formally. Accordingly, I would urge that you give us guidance for the certification of new HV systems by reexamining the E. coli K12 and submitting such a formal certification document.

11.) As member of the Working Panel for the American Society for Microbiology I am concerned with the possible requirement for certification of technicians and individuals who do recombinant DNA research. You may wish to give some thought to this as you evaluate the ASM report.

12.) Finally your document is well written and exceptionally well proofed. I only call these few typo's to your attention to aid you in revising any document that you produce. On page 33062, right hand column, line 13, word "interpreted" is misspelled. The "i" is missing. On page 33071, right hand column, line 16, "decontaminated" is misspelled. Finally, on page 33124, middle column, line 12, the word "very" is misspelled.

Again Don, I wish to compliment you for a job well done. I will be sending you under separate cover some information regarding the Bacillus subtilis system that I believe should be helpful to you in the final evaluation of the guidelines. I wish to get these general comments to you as rapidly as possible, however, and will delay the next series of comments until I have a chance to put a scholarly document together concerning the B. subtilis system.

Sincerely,

Frank

Chairman, Biosafety Committee

FEY:dd
Enc.
cc Dr. Roger C. Herdman
Mr. Donald K. Hess
President Robert L. Sproull

[Enclosures included (1) New York State bill S. 8019-A, Cal. No. 1127, A. 10398-A (Chap. 488, L. 1978, eff. 7/20/78), and (2) letter from Dr. W.J. Gartland to Dr. Frank E. Young, 5/25/78.]

Statement of the Honorable Douglas M. Costle
Administrator, Environmental Protection Agency

in the matter of: the Proposed Guidelines for the Conduct of Research Using Recombinant DNA -- September 15, 1978

Secretary Califano, Assistant Secretary Richmond, distinguished panelists--I am pleased to be able to submit this statement on the potential effects of research using recombinant DNA as it may impact on the environment. This opportunity for me and for other interested persons to inform you of our views is most welcome. While it is evident that the proposed revised guidelines on recombinant DNA research demonstrate that you are fully conscious of the enormous potential made possible by the use of recombinant DNA, they must also focus on control procedures to protect the lives and health of people and the environment from inadvertent effects of this new research procedure. The guidelines as originally proposed and now revised, have been carefully studied by a special subcommittee of the Environmental Protection Agency's Science Advisory Board, and in addition by scientists within EPA. Although these revised guidelines are less stringent than those previously developed by the National Institutes of Health, we tend to feel that they may be sufficient to safeguard human health from effects arising directly from the use of recombinant DNA.

However, we maintain that the original and revised guidelines are deficient with respect to protection of the environment. Information is not available on the possible extent to which our natural environment is in danger from inadvertant exposure to different and more complex forms of genetic material. We must take all necessary steps to prevent events which could allow release of recombinant DNA into the soils, air, waters, of natural environmental systems with consequent unknown impact on the biota of those natural systems. In fact, our Science Advisory Board, in a statement previously circulated within National Institutes of Health, noted the need to perform studies on the survival of host organisms, both prior and subsequent to insertion of novel genetic materials, in various soil, air, and water samples, and model ecosystems.

In this way knowledge about the effects of an accidental release of recombinant organisms can be obtained without the undesirable event of an accidental release.

The guidelines, as revised, offer virtually no protection to the natural environment both in terms of current and future research developments in this field. Amending and revising any set of guidelines are difficult and time consuming tasks. We do not necessarily request revision as much as the addition of materials which provide suitable environmental safeguards. We would like to see the Recombinant Advisory Committee that oversees these guidelines include representation of knowledgeable specialists in environmental processes and effects on ecosystems and their biota. Such persons might help to redirect research for those applications leading to potentially harmful environmental consequences. Future revisions of the guidelines must also include the needed environmental safeguards.

We note the provision for voluntary submittal of protocols by private parties, which do not come under the mandatory application of these guidelines. Our experience does not lead us to believe that voluntary controls provide effective deterrants. We hope, however, that all such parties will in fact, submit their protocols for review, and abide by the guidelines. It will not only afford protection to our citizens and our environment, it should serve as a valuable safeguard against potential liability from the impact of R-DNA research and application. In the absence of definitive control, this provision is helpful.

EPA does not desire to stifle recombinant DNA research. There is much benefit to be derived from its proper application. However, in summary I wish to state that we are greatly concerned that the research be confined to well controlled laboratory conditions and persons knowledgeable about safe handling of possibly pathogenic materials to preclude any chance for accidental release. The natural environment is inextricably related to the health and welfare of people. Thus, indirect health protection for people requires direct protection of the environment.

Thank you again for affording me the opportunity to present my views in this matter.

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20500

September 15, 1978

MEMORANDUM

TO: Peter Libassi
Julius Richmond
Henry Aaron
Don Fredrickson

FROM: Gil Omenn GSO

RE: September 15 Recombinant DNA Hearing

I was pleased to be invited to the Hearing. It was very well-run and generally constructive. I imagine that many of these arguments have been heard before, especially the rhetoric about who is paid to represent the "public"; on the other hand, a great many specific items were raised about the intent and wording of the proposed revisions of the guidelines, which I am sure will receive close scrutiny.

I hope that any further revisions based upon this Hearing and the many written comments can be made expeditiously.

Best wishes.

STANFORD UNIVERSITY, STANFORD, CALIFORNIA 94305

PAUL R. EHRLICH
BING PROFESSOR OF POPULATION STUDIES
DEPARTMENT OF BIOLOGICAL SCIENCES

September 15, 1978

Donald S. Frederickson, M.D.
Director
Department of Health, Education and Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Frederickson:

In my opinion as an evolutionist and environmentalist the potential benefits from recombinant DNA research are so great that it would be foolhardy to restrict such research largely on the basis of imagined risks. I approve of the continuing review of such research by competent scientists and favor the revision of the NIH Guidelines from time to time in accordance with the recommendations of the reviewing group.

Sincerely yours,

Paul R. Ehrlich

PRE:jlb

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DR DONALD S FREDRICKSON, DIRECTOR
NATIONAL INSTITUTE OF HEALTH
BETHESDA MD 20014

THE FEASIBILITY OF USING A. TUMEFACIENS TO IMPROVE MANY AGRICULTURALLY IMPORTANT PLANTS HAS BEEN DEMONSTRATED THIS ORGANISM IS A NATURAL EXCHANGER OF DNA WITH PLANTS THE POTENTIAL OF THIS SYSTEM CAN ONLY BE REALIZED BY ALLOWING EXPERIMENTS WHICH PERMIT RECOMBINANTS BETWEEN BACTERIAL AND PLANT DNA IN MY OPINION THERE IS NO HAZARD IN THESE EXPERIMENTS

PROFESSOR MILTON P GORDON
DEPT OF BIOCHEMISTRY
UNIVERSITY OF WASHINGTON

12:37 EST

MGMCOMP MGM

TO REPLY BY MAILGRAM, SEE REVERSE SIDE FOR WESTERN UNION'S TOLL - FREE PHONE NUMBERS

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

DEPARTMENT OF BIOCHEMISTRY
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Area Code 415
497-6161

September 15, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Building 1, Room 124
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I am writing in reference to the Proposed Revised Guidelines for recombinant DNA research. In general, I would anticipate that the proposed guidelines will be a marked improvement over the present obsolete and inadequate guidelines. However, I have the following objections to the proposed revisions.

1. The new P1 and P2 containment conditions are not significantly different. The difference between P1 and P2 should be approximately the same as the difference between HV1 and HV2, and this is clearly not the case. I think that there is a need for a low level physical containment for those organisms considered of minimal risk.

2. I object strongly to the escalation of the P1 and P2 containment rules. They should be made more stringent only if there is a demonstrated inadequacy in the present rules; I know of no such inadequacy. Unwarranted changes such as this one make administering a research laboratory much more difficult. And in addition, as a teacher, I am at a loss to explain to students and colleagues the need for the changes.

3. In section II-B-2-9-(16), the sentence "The laboratory shall be kept neat and clean." is totally ambiguous and should be dropped. Having a statement such as "Common sense shall be used in the laboratory." would be more useful.

4. The use of biohazard signs at the P2 level should be discontinued. they should be reserved for demonstrated biological hazards. There is a real danger that overuse of these signs in cases where workers know they do not apply will lead to the ignorning of all biohazard signs. A possible compromise might be to have universal "Hypothetical Biohazard" and "Real Biohazard" signs of different color and design.

5. A basic premise governing the original containment conditions was that all recombinants would initially be handled at a containment level much higher than was generally perceived necessary and that, with time and experience, these levels would be lowered. I strongly endorsed this concept at the Asilomar Conference. At the present time, we have had the most experience with recombinants of baker's yeast and Drosophila DNA in E. coli cells, and many tests have been conducted with them. Every viable DNA sequence of these two eukaryotes has been cloned in E. coli, and there is no indication that these recombinants pose any possible hazard to man or the environment. I think that it is time for recombinants of baker's yeast and Drosophila in E. coli K12 to be lowered at least to P1 containment.

6. The present guidelines frequently use the term recombinant DNA. The proposed revisions have replaced this term with organisms containing recombinant DNA. What is generally meant, however, is viable organisms containing recombinant DNA.

7. I strongly disagree with the proposed containment for recombinant DNA in higher plants. The P1 and P2 containment levels were designed for microorganisms. How can they be applied to a whole corn plant? How can one mouth pipette or generate an aerosol of a corn plant? I don't think that higher plants containing non-viral recombinant DNA should require any physical containment at all.

I was originally a strong supporter of the Guidelines and of the processes that generated them. I am no longer such a supporter and, in addition, I deeply regret my having been a co-signer of the original biohazard letter (Science 185, 303 (1974)) and a participant in the Asilomar Conference. I naively thought in those days that a logical procedure could be set up for generally handling hypothetical hazards that would not stifle creativity. I was wrong. The present Guidelines have been adequate in administering experiments that were being conducted before they were written, but they have been a disaster for new experiments. Novel experiments that are not explicitly covered in the present Guidelines have generally been prohibited. This prohibition has been enacted even though no hazard greater than for those experiments presently being conducted was even hypothetically evident. I can only conclude that the present Guidelines do not allow for novel and creative ideas, and it is not clear that the proposed revised guidelines are an improvement. The prohibition of novel ideas and creativity is totally

repugnant to the scientific process and to the American ideal. I do not think that the American people should have to pay such a price to contain imaginary hazards.

Sincerely yours,

Ronald W. Davis

RWD/lh

VETERANS ADMINISTRATION
DEPARTMENT OF MEDICINE AND SURGERY
WASHINGTON, D.C. 20420

SEP 18 1978

IN REPLY REFER TO: 15

Donald S. Fredrickson, M.D.
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

The Veterans Administration welcomes the opportunity to comment on the proposed revised guidelines for recombinant DNA research as published in the Federal Register, Vol. 43, No. 146, page 33042 to 33178, July 28, 1978. The VA very much prefers guidelines rather than regulations or legislation in this scientific area.

In general, the Veterans Administration finds the new guidelines thoughtfully conceived, satisfactorily flexible, and conservative enough to afford protection where it is needed. We welcome also the recognition that the individual institution is responsible for the conduct of recombinant DNA experiments.

It should prove helpful also that the opponents of DNA research must be prepared to show that the procedure they are protesting has a true potential for being unsafe. This shift in the burden of proof should minimize unwarranted interference with scientific progress.

Our comments suggesting reconsideration center around the various committees and their relation to the Director of the National Institutes of Health. We feel that the Recombinant DNA Advisory Committee properly has been assigned an important role and that great dependence is placed on its scientific judgment. Under these circumstances, it would be appropriate for other federal agencies engaged in DNA research to propose members for this Committee.

There is a question concerning the jurisdiction of various government agencies, including the Veterans Administration, over research funded and conducted by them including investigations by their own employees and in their own facilities. It is not clear what control the National Institutes of Health would have over such research. The Federal Interagency Committee on Recombinant DNA Research could provide coordination of policies in this area as suggested on page 33051 but it would have to have a much more active role than it has in the immediate past.

It would be preferable, we feel, to have a small committee consider waivers of prohibitions and other exceptions to the guidelines instead of vesting this function in the Director of the National Institutes of

"To care for him who shall have borne the battle, and for his widow, and his orphan."—ABRAHAM LINCOLN

Health. Such a move would remove pressures on the Director, allow wider scientific and legal imput, and should not interfere with the research. It would be possible to constitute a committee to consider waivers of prohibitions from other federal agencies with membership from the federal research community of those agencies. Since requests for waivers would not be numerous from within the federal government, a separate committee to consider them should not prove burdensome.

We very much appreciate the opportunity to comment on the proposed guidelines and look forward with interest to their eventual publication.

Sincerely yours,

James C. Crutcher

JAMES C. CRUTCHER, M.D.
Chief Medical Director

CARNEGIE INSTITUTION OF WASHINGTON
DEPARTMENT OF EMBRYOLOGY
115 WEST UNIVERSITY PARKWAY
BALTIMORE, MARYLAND 21210
TELEPHONE: 467-1414

September 18, 1978

Dr. Frederickson,
The Director
National Institutes of Health
Bethesda, Md. 20014

Re: Proposed revised guidelines for recombinant DNA research

Dear Dr. Frederickson,

I wish to comment briefly on the revised NIH Guidelines elaborating on some of the remarks that I made in my public testimony on September 15. On the whole the revisions are a good step toward a more rational set of procedures, the existing guidelines being unnecessarily strict.

1. There is no reason not to make all shot gun experiments P2 EK1 and to permit the cloning of viruses and viral fragments. We simply must admit that these pieces of DNA in E. coli cannot be more dangerous than their original source. This statement has irrefutable logic as an assessment of potential risk.

2. It is logical and sensible to give much authority to local biohazard committees. The rules are set forth in such detail that there can be very little worry about uneven interpretation by different committees. The burden on the NIH committee seems overwhelming at present. I agree that individuals who work with recombinant DNA should not be members of these committees. However it is rediculous to populate a committee designed to control biohazards with lay people having no understanding of the issues. The members should include knowledgeable microbiologists, epidemologists, public health specialists and yes, biochemistry and even molecular biologists.

3. Case by case analysis of experiments following outside the guidelines is welcome although it means more burden for NIH.

(Conintued -- page 2.)

I really congratulate those who drew up these revised guidelines. They show enormous attention to detail and reason. I hope the revisions continue periodically, and perhaps in the near future they will be thrown out altogehter, and it will be possible to treat recombinant DNA research as just any other problem in medical microbiology.

Sincerely yours,

Donald Brown

Donald D. Brown,
Director, Department of Embryology
Carnegie Institution of Washington

DDB:GS

STATE OF CALIFORNIA — HEALTH AND WELFARE AGENCY

EDMUND G. BROWN JR., Governo

DEPARTMENT OF HEALTH SERVICES
714/744 P STREET
SACRAMENTO, CA 95814
(916) 445-1248

September 18, 1978

Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Sir:

These comments are directed to the proposed guidelines for Recombinant DNA Research as printed in the Federal Register of July 28, 1978.

The California Department of Health Services considers these guidelines unsatisfactory in five areas.

1. The proposed guidelines as presently constituted fail to embody emergency or other intervention plans to involve state health agencies in minimizing any health risks which may attend to any noncompliance, particularly that which results in a "spill" or otherwise exposes the population to potentially harmful recombinant organisms. Presently the Guidelines simply require a report to the local Biosafety Committee and NIH. (Section IV-A-4-h)

   Recommendation

   Require that any research which is found to be out of compliance with NIH be reported to the California Department of Health Services or a local representative; and that any release of recombinant organisms, regardless of presumptive nonpathogenicity, be reported to the proper health authorities.

2. As presently drafted, the Guidelines lack specificity in establishing the conditions for minimizing risks once an accident has occurred.

   Recommendation

   Include specifications for cleanup procedures to be followed should there be a spill or accidental release of organisms into the environment. Such procedural safeguards should incorporate the suspected pathogenicity or hazard posed by the released organism.

3. The Guidelines do not establish a central clearing house which would record and monitor the nature and kind of organisms being used in recombinant DNA work and collect data regarding the safety record of particular laboratories.

   Recommendation

   Require an appropriate agency within NIH and a State affiliate of the California Department of Health Services or Cal-OSHA to maintain such data, including accurate records of workers in recombinant DNA work, with particular regard to the incidence and severity of possible work related illness; or, require that special reporting requirements be met by research laboratories with their respective Biosafety Committees, who in turn will file reports with State or local agencies.

4. While the new proposed guidelines acknowledge the problem of certification (page 33132) and considerable more input from laboratory health experts, they still do not require the special training procedures which are now standard for certain laboratories doing work with pathogenic organisms.

   Recommendation

   Specify that lab workers in P2 and higher facilities take and pass certain training courses, or demonstrate equivalent competency, prior to working directly with recombinant DNA organisms. A centralized and uniform certification process would be extremely desirable for P3 and P4 level workers. The State presently has such a program, and has the requisite expertise (Dr. Edwin Lennette) to organize and conduct Statewide training.

5. The policy on noncompliance is vague and weak. It invites too much latitude in defining penalties by encouraging discretion to be used, from exoneration to full penalties, without mention of due process to injuried parties, particular-y workers.

   Recommendation

   Section IV-D-1-b on Page 33087, remove the word "may" and replace with "shall ... upon an affirmative finding after due process, that a willful violation has in fact occurred." Negligence may result in similar suspension, limitation, or termination of NIH funds. It should also be stated that federal action does not preclude state action where activities in question violate state statutes or regulations.

If you have any questions regarding our concern for wider discretionary powers assigned to local health authorities to monitor and oversee recombinant research, please contact Marc A. Lappe, Ph.D. at (916) 445-8706.

Sincerely,

Beverlee A. Myers

Beverlee A. Myers
Director

A Statement on Risk Assessment

Arthur J. Schwartz
Associate Professor
Department of Mathematics
University of Michigan
Ann Arbor, Mich.

In volume 43, number 146 on page 33056 of the Federal Register, the director of the NIH states "The work of Robin Holliday in assessing statistical probabilities of biological accidents is also noteworthy (see appendix P of the October 1977 Environmental Impact Statement.)". Earlier in the section on risk assessment (same page) he states "many commentators advocate more studies in risk assessment. It has been maintained that assumptions about biological containment may not be valid and that all components should be tested. Concern has been expressed that the biological containment safety systems may fail altogether."

I pointed out during a hearing of the NIH in December 1977 that the Holliday article was weak on a number of points and far from authoritative. To begin with the probabilities that Holliday computed were a priori probabilities at best and more likely a collection of hunches and guess work. The term "statistical probabilities" would seem to imply a posteriori probabilities based on actuarial evidence. The article of Holliday presents no such figures.

The methodology used by Holliday makes blanket, unwarranted and imprudent use of the assumption of statistical independence. This error generally creates an unduly optimistic picture. Holliday considers only a few accident scenarios and ignores the very serious problem of design failure and outside disturbances not to mention totally unforeseen scenarios.

I have consulted with other probability theorists, statisticians, actuarial scientists, and health physicists. I can find no theoretical or empirical support for Holliday's assertions.

September 16,1978

THE UNIVERSITY OF ARIZONA

HEALTH SCIENCES CENTER
TUCSON, ARIZONA 85724

COLLEGE OF MEDICINE
UNIVERSITY DEPARTMENT OF BIOCHEMISTRY
(602) 626-6025

September 18, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20016

Dear Dr. Fredrickson:

I have read a copy of the Proposed Revised Guidelines for Recombinant DNA Research (Federal Register 43, 33042-33178). I agree with the general nature of the proposed changes. The two major factors which make these changes valid are a) the general inability of eukaryotic genes to be expressed in prokaryotic cells and b) the inability of *E. coli* K-12 to effectively colonize the human gut.

There are, however, two inconsistencies which I noticed in the proposed changes to the guidelines. These are the conditions required for cloning mammalian DNA (other than primates) and bird DNA in a shotgun experiment. The guidelines state this should be performed under P2-EK2 conditions. I believe it should be changed to P2-EK2 *or* P3-EK1. The concept of allowing the biological containment to be reduced when the physical containment is increased has numerous examples in the guidelines. Specifically the combination of P2-EK2 *or* P3-EK1 containment is found for experiments 6, 12, 13, 19, 25, 42 and 43 (pg. 33133 to 33135 of the proposed revisions to the guidelines). It seems an oversight that a similar combination of containment is not allowed for birds and mammalian (non-primate) shotgun experiments.

Sincerely yours,

Larry A. McReynolds

Larry A. McReynolds

LAM/cs

MEMORIAL SLOAN-KETTERING CANCER CENTER

1275 YORK AVENUE, NEW YORK, NEW YORK 10021

September 18, 1978

Dr. Donald S. Fredrickson
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I am writing on a matter of great importance to science. Work has been held up in recombinant DNA studies because of guidelines and uncertainties they have generated.

In the further development of regulations with respect to recombinant DNA research, I urge that all steps necessary be taken to retain the development of national guidelines and possible future modifications of them under the aegis of NIH. The guidelines should not be imposed by a less knowledgeable group no matter how good their intentions might be. NIH is in the best position to establish appropriate guidelines for research in that area because of its experience, the expertise readily available to it and the probability it is, and will be, funding most of the research on recombinant DNA.

Although I am not personally engaged in such research, I believe strongly that following the course recommended above will be best for that field and for science in general.

Sincerely,

C. Chester Stock

C. Chester Stock, Ph.D.
Vice President and Associate Director
for Administrative and Academic Affairs

[A-171]

MEMORIAL HOSPITAL FOR CANCER AND ALLIED DISEASES
SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
SLOAN-KETTERING DIVISION, GRADUATE SCHOOL OF MEDICAL SCIENCES, CORNELL UNIVERSITY

OARDC

Ohio Agricultural Research and Development Center

WOOSTER, OHIO 44691

TELEPHONE (216) 264-1021

DEPARTMENT OF
PLANT PATHOLOGY

September 19, 1978

Mr. Richard Riseberg
DHEW Office of General Consul
National Institutes of Health
Bldg. 31, Room 2B50
Bethesda, MD 20014

Dear Mr. Riseberg:

When I testified at the public hearing on the Proposed Revised Guidelines for Recombinant DNA Research on September 15, I submitted only a summary of my comments. Enclosed you will find 20 copies of my complete statement for your use.

I have two additional comments on the revised guidelines concerning the proposed list of "gene exchangers". First, crown gall caused by Agrobacterium tumefaciens has become a popular model system for many molecular biologists studying cancer, gene transfer between prokaryotes and eukaryotes, and plant cell differentiation. The ommission of Agrobacterium radiobacter from the list of "gene exchangers" is serious because this species is an avirulent form of A. tumefaciens and is distinguished from it solely on the basis of tumorigenicity. Thus, an A. tumefaciens strain which has lost its virulence plasmid could be classified as A. radiobacter. Second, I forsee that there will be a need to add the genus Xanthomonas to the list of exchangers after more work has been done on plasmid exchange between it and P. aeruginosa and E. coli. It would be helpful, therefore, if the guidelines were more specific on what critera must be satisfied to place an organism on the "exchanger" list.

I appreciated the opportunity to express my views at the public hearing and hope that the new guidelines will be implemented soon.

Sincerely,

David L. Coplin

David L. Coplin
Assistant Professor

DLC:jlh
Enclosure

[Enclosure is printed with written statements submitted by witnesses at HEW public hearing.]

Amherst, Massachusetts
September 19, 1978

Dr. Donald Fredrickson
Director, NIH
Bethesda, Md. 20014

Dear Dr. Fredrickson,

As members ofthe Tonw of Amherst Study Committee on recombinant DNA research, appointed by a mandate from last year's Town Meeting, we have been following with concern and interest the evolution of the guidelines for recombinant DNA research. The Town adopted the NIH guidelines to be the standard for all recombinant DNA research done within town limits.

We are writing this letter as individuals, and our concern is that the latest revisions are lacking adequate experimental data. We realize that as yet no accidnets have been detected as a result of recombinant DNA research, but we also realize that the research is very young and that the effects of escape from containment or contamination might be slow in becoming evident.

We urge that more risk assessment be done and more evidence made available to the public before the guidelines as now revised are adopted. We feel that acceptance of the revised guidelines at this time would be premature.

Also, we feel strongly that before any new guidelines are adopted and become the de facto standards a full environmental impact statement including the revisions be made public.

As committee members assessing the potential use/misuse and risk/benefits of this research full access to the above information is essential for responsible evaluation of recombinant techniques and their possible effects on the environment and in society.

Sincerely,

Terri Goldberg
Terri Goldberg
Paul Newlin
Paul Newlin

Natural Resources Defense Council, Inc.

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COMMENTS OF THE

NATURAL RESOURCES DEFENSE COUNCIL, INC.

ON THE PROPOSED REVISION OF

THE NATIONAL INSTITUTES OF HEALTH'S

GUIDELINES ON RECOMBINANT DNA RESEARCH

(43 FR 33042, July 28, 1978)

Marcia Cleveland, Esq.
Louis Slesin, Ph.D.

September 19, 1978

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SECTION I

I. INTRODUCTION

In his introductory statement, the Director of the National Institutes of Health (NIH) asserts that five years after the molecular biology community first expressed concern about the risks of recombinant DNA, " ... no evidence has come to light of a product created by these techniques that has been harmful to man or the environment." He concludes, "At the least, there is growing sentiment that the burden of proof is shifting towards those who would restrict recombinant DNA research." (43 FR 33044). This syllogism, that NIH's failure to find evidence of harm requires a shift in the burden of proof, is the central reason for the proposed weakening of the NIH Guidelines for Recombinant DNA Research (43 FR 33042, July 28, 1978; hereafter proposed revised guidelines).

NIH's logic is faulty; the failure to find evidence of harm primarily reflects NIH's failure to look. No comprehensive risk assessment program for recombinant DNA has ever been proposed or initiated. The appropriate response to the present dearth of information about the risks is not to reduce required levels of containment and ease procedures for enforcement of the guidelines, but to initiate and fund research that will provide a base for a sounder evaluation of risks.

Rather than shifting the burden of proof to those who question the safety of recombinant research, NIH should fully assume its statutory duty of conducting research into the causes and preventions of disease.[1/] It is irresponsible for NIH to use its authority to fund biomedical research which promotes the use of recombinant techniques without also supporting research into the adverse effects the use of these techniques may have. What is now known about genetic recombination raises serious questions about possible risks; NIH is the appropriate party to assume the burden of answering them.

Until a comprehensive risk assessment program is completed, the only prudent course is to require containment at least as great as that provided by the 1976 NIH Guidelines. While the 1976 guidelines do not provide full protection from potential risks, they are generally stricter than the proposed revised guidelines. Furthermore, the 1976 guidelines have been in use for two years and continued use, with some of the improvements made by the proposed revision, will not disrupt research now underway.

1/ 42 U.S.C. § 241(a)

II. SUMMARY OF COMMENTS AND RECOMMENDATIONS

In these comments the Natural Resources Defense Council, Inc. (NRDC) addresses two types of issues: (1) the inadequacy of the scientific evidence on which NIH relies in relaxing the guidelines; and (2) the weakness of the proposed administrative and enforcement provisions.

Available scientific information on the risks of recombinant DNA research is still sketchy and incomplete. No conclusions can be reached about the safety of this type of research until a comprehensive risk assessment program has been completed.

The evidence NIH cites as a basis for lowering containment levels does not support the extensive reduction in protection in the proposed revised guidelines. Much of the evidence has never been published or is available only in summary form. By withholding the scientific basis for its decision, NIH has prevented critical review of the data by the scientific community and has effectively excluded the public from having a say in the policies behind these proposed revisions. While some of the new experimental findings relieve some concerns, they also show that there are some potentially serious risks associated with some recombinant DNA research. In our detailed technical comments we identify potential risks and scientific issues that need to be resolved by further research. We also recommend stricter containment for some kinds of experiments.

The proposals to decentralize administration of the guidelines and increase the discretion of the Administrator

and the Institutional Biosafety Committees (IBCs) exacerbate the conflict of interest problems inherent in the system of self-regulation the guidelines rely on. These conflicts of interest inevitably lead to poor enforcement. Current regulations for training and monitoring laboratory workers are too vague. Finally, NRDC recommends some changes in the membership and activities of the biosafety committees and improved sanctions.

NRDC makes the following major recommendations:

1. NIH should initiate and fund a comprehensive risk assessment program to provide a scientific basis for defining appropriate containment requirements for recombinant DNA experiments.
2. NIH should continue use of the 1976 guidelines with the strengthening changes proposed for the revised guidelines. (See §§ VI-A, VI-D-1 <u>infra</u>)
3. In the absence of recombinant DNA legislation, the Department of Health, Education and Welfare should establish standards for future revisions of the guidelines rather than leaving revisions to the discretion of the Director of NIH. Such standards should tie revisions to the results of the risk assessment program. Standards should be developed for the exercise of other discretionary functions by NIH and the IBCs.
4. Institutional Biosafety Committees should not have primary responsibility for enforcing the guidelines.

5. NIH should establish training and monitoring programs for laboratory workers.

III. A COMPREHENSIVE RISK ASSESSMENT OF RECOMBINANT DNA RESEARCH IS NEEDED

The recombinant DNA debate is now five years old; while some specific risk experiments have been conducted, neither NIH nor any private group has proposed or done a comprehensive risk assessment. Even though the guidelines are based on presumed or potential risks, efforts to test these presumptions has been piecemeal. While some of the risks are too speculative to be evaluated by experiments, many of the risk questions can be resolved by more research. A detailed research plan must be formulated which explains what the uncertainties are, which experiments can resolve them, who will carry them out, and how long it will take. Without such an assessment we cannot endorse a general reduction in containment levels.

Meetings have been convened to discuss specific types of risks (e.g., at Falmouth and Ascot), but their scope has been limited to a few discreet topics. The larger framework into which the Falmouth and Ascot deliberations can be placed is missing. At Falmouth

a six-point research plan was proposed to investigate further the nature and extent of certain types of risks.[2/] To our knowledge, this plan has not been implemented.

IV. BARRIERS TO PUBLIC REVIEW OF TECHNICAL INFORMATION

At the last public hearing on these guidelines in December 1977, Professor Robert Sinsheimer found himself unable to comment on that round of proposed revisions because of NIH's "extensive reliance on unpublished data."[3/] We find ourselves in the same unfortunate position with respect to the new assertions that recombinant DNA experiments carried out under the guidelines present negligible risk.

Advocates of a relaxation cite three important sets of data:

(1) The proceedings of the Falmouth conference held in June 1977;

(2) The deliberation at the United States-European Molecular Biology Organization (US-EMBO) workshop held in Ascot in January 1978;

(3) The Martin-Rowe experiments.

Leaving aside the specific findings of these discussions and experiments, which are discussed in §§ V and VI *infra*,

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2/ *Journal of Infectious Diseases*, *137*, (1978) pp. 704-714. The proceedings of the Falmouth Conference were published in this, the May, issue of the Journal. A large number of the references we cite below will be to this issue; in the interests of simplicity, we shall simply refer to the appropriate page number, preceded by an 'F' to designate the Falmouth proceedings.

3/ N. Wade, *Science*, *177* (1978), 31.

the process followed by the expert scientific communities has made it extremely difficult for the public to participate in the recombinant DNA rulemaking:

(1) The Falmouth conference proceedings were published in the May 1978 Journal of Infectious Diseases, just a few weeks before the revised guidelines were published for public comment. This left little time for people to read and digest the technical papers.

(2) The proceedings of the Ascot, US-EMBO workshop have not been published. A summary report was issued in the March 31, 1978 Federal Register. This failure to open the proceedings to public scrutiny is especially important since none of the American critics of the NIH regulatory procedures and risk assessments were invited to attend. Nor did the critics have an opportunity to review the Ascot report at the subsequent April 6-7, 1978 Recombinant DNA Advisory Committee Working Group.

(3) The much touted Martin-Rowe experiments on the potential infectivity of polyoma DNA when it is inserted into a plasmid has never been published. It is cited in the Environmental Impact Statement as Israel et al. (1978a), "in preparation."

Thus, we are left with the nagging impression that these revisons are being rushed through the public review process.

To the dismay of all participants, the recombinant DNA controversy has become overheated and polarized. The public is wary and in most instances does not understand what the risks are about and how they can be reduced. This situation is only aggravated when the NIH fails to make all the relevant facts available, fails to afford the critics an opportunity to be party to the deliberations, and fails to allow the public time to digest and review the complex information required for an informed evaluation.

V. AVAILABLE EVIDENCE DOES NOT SUPPORT A GENERAL LOWERING OF CONTAINMENT LEVELS; MANY QUESTIONS OF RISK ARE STILL UNRESOLVED

Contrary to what seems to be the prevailing dogma, the experimental results and scientific meetings leave many unanswered issues about risk to be resolved.

While there was general agreement at the June 1977 Falmouth conference on "Risk Assessment of Recombinant DNA Experimentation with *Escherichia coli* K12" that *E. coli* K12 could not be inadvertently converted into an epidemic human pathogen by recombinant DNA experimentation (F: 609-714; esp. 699-703), the participants at that same conference did identify several areas where there remains reason for caution. These include the following possibilities: (i) recombinant plasmids might be transferred to more virulent strains of bacteria (F: 648-654; 686-687; 668-675; 704-714 and n.4); (ii) bacteria or viruses containing recombinant DNA could

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4/ E.S. Anderson, *Nature*, *255* (1975), 502-504.

cause autoimmune diseases (F: 663-667); (iii) viral DNA cloned in E. coli may retain its infectivity (F: 704-714); and (iv) the virulence of experimental E. coli strains may be increased by recombinant DNA, thus endangering the people directly exposed to the experimental bacteria (F: 704-714). As we have already noted, several excellent experiments to assess these risks were proposed at the Falmouth conference. Others need to be proposed and carried out to assess the hazards that may be presented to a wider range of organisms in the biosphere.

Knowledge about the possibility of a transfer of recombinant plasmids to wild bacteria has been overestimated, and the risks prematurely discounted. Until the natural processes of genetic transfer are better understood, we shouldn't place too much confidence in the integrity of biological containment. As Professor King of MIT commented at the Falmount conference:

> The danger of recombinant DNA research is not one of making K12 into a pathogen; this argument has been raised as a straw man. As Dr. Anderson mentioned, the real question is the transfer of genes into the indigenous flora. This flora is already adapted to the host. The ecological problem is the transmission and routing of plasmids. (F: 701)

And, as Professor King and Professor Goldstein of Harvard Medical School wrote to NIH's new Recombinant DNA Technical Bulletin:

> Though there was general consensus [at Falmouth] that the conversion of E. coli K12 itself to an epidemic strain is unlikely (though not impossible) on the basis of available data, there was not consensus that transfer to wild strains is unlikely. On the contrary, the evidence presented indicated that this is a serious concern. 5/

There are several reasons to be wary of such transfers. Wild strains of E. coli that do not cause diarrhea are the major source of both community- and hospital-acquired infections in the United States; and diarrhea-causing strains are more prevalant in developing nations. The most common community-acquired E. coli infections requiring hospitalization are those of the urinary tract, lower respiratory tract, and skin (F: 634-638). Nondiarrheagenic strains may also colonize the gut but are not pathogenic there.

Generally, we conclude that there needs to be more study of gene transfer in the environment. In our section VI.E below, we will present the technical basis for our concern that novel DNA may in fact be incorporated in wild strains and make explicit recommendations to enhance the safety of many experiments.

In addition we wish to echo Professor Sinsheimer's repeated concern that the NIH guidelines are derived from an "extraordinary anthropocentric" point of view.6/ The reliance on the Falmouth deliberations compound this narrow interpretation of the hazards. The Falmouth conference only addressed the risks of E. coli to humans and not to the diverse microorganisms which may be susceptible to interaction with novel genetic combinations.

5/ Recombinant DNA Technical Bulletin, 1 (Fall 1977), 24.

6/ N. Wade, Science, 201 (1978), 601.

Similarly, preliminary word on the Martin-Rowe experiments suggests both positive and negative implications concerning the potential risks of certain cloned DNAs. (Again, we are unable to make definite statements since the results have yet to be published.) On the positive side, the work of Drs. Martin and Rowe indicates that polyoma DNA inserted into a plasmid is not infectious. On the negative side, their initial results show that polyoma DNA cloned in E. coli retains its infectivity in the linear form. (The DNA was administered orally and by injection.) Thus, as long as the DNA is in a circular form it is non-infectious, but a chance cut in the plasmid could render it infectious!

The question of the hazards associated with recombinant DNA experiments is extremely complicated. The expert community do themslves and the public a disservice by oversimplifying the known facts and proclaiming safety from risk in the absence of positive and published experimental evidence.

VI. SPECIFIC TECHNICAL COMMENTS AND RECOMMENDATIONS

A. Scope

NRDC supports the extension of the guidelines to experiments which incorporate synthetic DNA segments into DNA molecules (§ I-B of the guidelines). NRDC also supports application of the guidelines to all institutions which receive NIH funds regardless of whether the recombinant research is NIH supported. (§ I-C).

We also favor extension of the guidelines to industry. The establishment of a voluntary registry for private industry is a step in the right direction (43 FR 33044). But as we have argued in other comments and the NRDC and EDF petition, the guidelines should be promulgated as binding regulation applicable to all parties conducting recombinant DNA research under the authority of the Public Health Services Act.[7/]

B. Prohibitions

Prohibitions in §§ I-D-3 and I-D-5 allow the creation of pathogens and the transfer of drug resistance to pathogenic organisms if such combinations are known to occur "naturally." This ignores the fact that such "natural" combinations can be either extremely rare or extremely toxic. For example, though gonorrhea has been treated with penicillin for many years, a strain of gonococcus with resistance to the drug has only recently been found. This is no reason to sanction

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7/ 42 U.S.C. § 264.

the intentional creation of such drug-resistant, pathogenic organisms. Therefore, the prohibitions should apply to such recombinations regardless of whether they are naturally occurring or not.

C. Exemptions

1. The exemption in § 1-E-4 for experiments which would combine DNAs from natural exchangers of chromosomal markers is not advisable at the present time. (A list of exchangers is provided in Appendix A, 43 FR 33089.) Several problems are inherent in this proposed exemption. Data on exchange between some organisms on the list is flimsy or non-existent. For example, exchange has not been documented between *Hafnia* and *Edwarsiella* or between *Salmonella* and *Pseudomonas*. Only four species of *Pseudomonas* are known to exchange with *E. coli*. Similarly, exchange has not been demonstrated to occur between several of the plant pathogens listed.

Many of the species included in Appendix A are known pathogens. *Salmonella*, *Shigella*, *Klebsiella*, and enteropathogenic *E. coli* are Class 2 etiologic agents; *Pseudomonas pseudomallei* is a Class 3 agent. The standards for handling these organisims should be applied to the handling of bacteria containing DNA from these organisms, particularly since § I-E-4 places no restrictions on the use of readily transmissible vectors or healthy host strains.

The inclusion of several plant pathogens in Appendix A does not provide sufficient protection for plants. Caution

is in order because of possible changes in the host range and ecology of hybrid pathogens created by extracellular recombination. The inclusion of plant pathogens is also inconsistent with the exclusion of human pathogens such as Vibrio cholerae which are known to exchange plasmids containing chromosomal genes with E. coli and which have been excluded from the list of exempted species for good reason. Additionally, the ecological impact of an increased rate of exchange facilitated by recombinant DNA experimentation cannot be assessed.

2. Nor can we agree with the exemption in § I-E-1 for DNA that has been extracted from host cells. Such DNA is novel in that it would often contain sequences and genetic functions from widely separated species. As we have already noted, initial results of the experiments of Drs. Rowe and Martin indicate that polyoma DNA cloned in E. coli retains its infectivity in the linear form. It seems clear, therefore, that certain cloned DNAs need special handling for safety.

Experiments using cloned DNA will be conducted in laboratories in which bacterial contamination of buffer solutions and cultures is a common occurrence and where healthier strains related to crippled host strains may be commonly used. Consequently, the possibility of genetic transformation must be avoided. Transformation and transfection of prokaryotic and eukaryotic cells have been reported to occur both in vivo and under extreme conditions in the

laboratory. (F: 668-675, 704-714, and n.8).

Indeed, Griffith's original demonstrations of transformation was carried out by injecting mice with both nonvirulent and heat-killed Pneumococcus.[9/] Evidence is accumulating from in vitro experiments that plasmids exhibit a range of efficiency of transformation and that the efficiency is generally quite low (F: 668-678 and n. 10). Though it has been found to occur in animal hosts, Curtiss has concluded that " ... it is ... unlikely that transformation would be a very significant factor for gene flow in nature for most gram negative organisms."[11/] The ability of most bacteria to exchange DNA by this process is unknown and the mechanism of transformation is unknown.

Maturin and Curtiss have shown that DNA is rapidly degraded by nucleases in the small intestine of rats, thus providing a measure of confidence that DNA does not pass through mammals intact.[12/] Hoskins has found that one

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8/ A. H. Sturtevant, A History of Genetics (Harper and Row, New York, 1965); G. S. Stent, Molecular Genetics (W. H. Freeman and Co., San Francisco, 1971); M. J. Wigler et al., Cell, 11 (1977), 223-232; M. J. Bibb et al., Nature, 274 (1978), 398-400; R. Curtiss III, Annual Review of Microbiology, 70 (1976), 507-533; E. Rothenberg et al., Nature, 269 (1977), 122-126; and N. J. Maitland and J. K. McDougall, Cell, 11 (1977), 233-241.

9/ Stent, op. cit.

10/ Bibb et al., op. cit.

11/ Curtiss, op. cit.

12/ L. Maturin Sr., and R. Curtiss III, Science, 176 (1977), 216-218.

milligram per day is the upper limit for the amount of high molecular weight DNA excreted by a healthy American. (F: 694-698). It would seem prudent to provide protection for the environment which is equivalent to that provided by the mammalian small intestine., That is, naked recombinant DNA should be degraded and solutions containing it should be decontaminated before disposal.

D. Physical Containment

1. We endorse the banning of mouth pipetting under P1 conditions.

2. §§ II-B-1-a-(9), II-B-2-a-(12), and II-B-4-a-(16) mandating insect and rodent control programs on recombinant DNA labs are too weak. These sections should specify that the laboratories where recombinant DNA experiments are conducted "shall be free of insects and rodents which are not used as experimental animals." This was one of the major public concerns that emerged from the debates over recombinant DNA research in Cambridge, Massachusetts. Such insects provide a possible means of escape for organisms containing recombinant DNA molecules. The public deserves to know that important and sometimes expensive containment measures will not be breached by household pests.

E. Genetic Transfer: Implications for Physical and Biological Containment

Several findings are relevant to the problem of genetic transfer. (See detailed discussion in § IX.) Though it has been shown that *E. coli* K12 does not colonize the gut in the

absence of selection and X1776 will not colonize germ-free mice, both strains survive passage through the intestinal tract of animals. (F: 624 and n. 13). Colonization improves the likelihood of conjugational transfer in the gut but it is not a prerequisite. (F: 686-687). Dr. Smith noted at the Falmouth conference that conjugational transfer has been observed in animals when the donor and recipient strains are good colonizers of the alimentary tract and plasmid transmission is also efficient *in vitro*. (F: 711-712). Transfer was observed between *Salmonella* and *E. coli* and between different strains of *E. coli*. Transfer to *E. coli K12* has been observed in the rumen of fasting sheep. (F: 711-712). The gut of an animal or person is not the only environment in which transfer might occur. (F: 712).

Dougan, Crosa and Falkow presented a paper in Falmouth on the mobilization of the plasmid ColE1 and its derivatives. (F: 676-680). Mobilization of nonconjugative plasmids, such as ColE1 of *E. coli*, can be mediated with high efficiency by coresident conjugative plasmids, such as R or F factors. This process requires a triparental cross. Mobilization is also dependent in part on genes located on the nonconjugative plasmids, for example, on the mob locus on ColE1. (F: 676-680 and n. 14). The mob- phenotype reduces the frequency of

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13/ C. L. Wells et al., *Nature*, 274 (1978), 397.

14/ G. Warren and D. J. Sherratt, *Molecular and General Genetics*, 151 (1977), 191-194.

mobilization of ColE1 by R1drd19 by about five orders of magnitude. (F: 676-680). Derivatives of ColE1, including the recombinant DNA vectors pMB9, pBR313, and pBR322, contain deletions which overlap the mob locus. These deletions can be complemented in trans by ColE1 and ColK. Consequently, if a cell harbors both a mob- and a mob+ plasmid, both can be mobilized at high efficiency by a conjugative plasmid. The mob- phenotype of pBR322, for example, would be masked by ColE1. (F: 676-680).

In assessing the probability of conjugational plasmid transfer, it is important to use wild bacterial strains in the experimental crosses, because differences in the surface characteristics of wild and laboratory strains may influence the probability of multiple matings.[15/] The frequencies of mobilization by R1drd19 reported by Dougan, Crosa, and Falkow (F: 676-680) ranged from 10^{-1} and 10^{-2} for ColE1 and RSF2124 to 10^{-6} for pBR313 and pBR322 in both E. coli and healthy X1776. These frequencies may be higher or lower than frequencies resulting from matings of wild bacterial strains.

If the rate of infectious transmission is sufficiently high, plasmids can be maintained in a bacterial population even if they confer a selective disadvantage on the host organism. (F: 710-711).

15/ J. W. Costerton, et al., Scientific American, 238 (1978), 86-95.

Transduction is another process by which recombinant DNA may be transferred from the laboratory to wild populations of bacteria. Little is known about the occurrence of transduction in the wild. Most strains of E. coli are sensitive to the generalized transducing phage P1, but the distribution of this phage in the environment has not been studied. (F: 711). Anderson reported that one out of 114 strains of E. coli isolated from 38 human subjects was sensitive to infection by phage lambda. (F: 686-687). Lambda lysogeny was not observed in this strain. More study is needed to determine whether or not transduction contributes to bacterial gene flow in the wild.

Though E. coli K12 and X1776 have vastly different capacities to survive in many environments; they have similar capacities to proliferate in and kill experimental animals when injected into various tissues.[16/] Wild strains are 1,000 to 10,000 times more virulent than these laboratory strains in injection experiments. The LD_{50} for K12 and X1776 when injected into mice is about 10^8 to 10^9 bacteria; this number would be contained in one ten-thousandth of a milliliter of bacterial pastes routinely handled in microbiological experiments.

Therefore, we recommend:

(a) Phsycial containment levels should not be compromised until biological containment is better understood. This is especially important in considering the change from P4 to P3 and

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16/ S. B. Levy et al., Nature, 274 (1978), 395.

P3 to P2 conditions, because the difference between these levels of containment is large. Additionally, the substitution of biological for physical containment measures, as embodied in the proposed revisions of the guidelines, has not been demonstrated to be valid or effective.

(b) In concert with further study of genetic transfer mechanisms, several measures can be taken immediately to guard against bacterial contamination of recombinant DNA experiments. These additions to § II-D might include: (i) the mandatory incorporation of control plates or broth cultures into recombinant DNA experiments to insure the identity of hosts and vectors and (ii) the physical isolation of experiments requiring different levels of biological containment. These measures are easily implemented in the laboratory, and they would be an effective barrier to the inadvertent contamination of cultures, a not uncommon occurrence in microbiology laboratories.

F. Experiments with Viral DNA

The reason for the containment levels which are currently mandated for experiments with viral DNA is the possibility that a harmful virus or viral product would gain an extended host range when cloned in a novel host organism. The previously mentioned results of experiments carried out by Drs. Rowe and Martin indicate that this concern is justified for the cloning of complete viral genomes and hybrid genomes in bacteria.

The formation of viral hybrids is an important model for

the evolution of viruses with expanded host ranges. 17/ Lear discusses a case in which the combination of a baboon virus and a mouse tumor virus resulted in a hybrid with the unexpected ability to cause tumors in mice, dogs, chimpanzees, and baboons, and also to infect human cells in culture.18/ The reduction in containment levels mandated for the cloning of viral DNA using eukaryotic viral vectors and viral complimentary DNA in prokaryotic host-vector systems is, therefore, a bold step. (See Tables III and IV, pp. 33079 and 33083.) The stipulation that some experiments will be assigned containment levels on a case by case basis ignores the need for minimum standards which can serve as a guide for research workers.

We therefore strongly recommend that specific biological and physical containment levels be assigned for experiments with hybrid viruses. In addition, caution should be exercised when productive viruses are used as vectors for recombinant DNA experiments.

G. Shotgun Experiments

The proposed reductions in containment levels mandated for shotgun experiments are quite substantial. They are based on a new confidence in the integrity of host-vector systems, the safety of cloning complete viral genomes, and the necessity

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17/ M. M. Kaplan and R. G. Webster, Scientific American, 237 (1977), 88-106.

18/ J. Lear, Recombinant DNA: The Untold Story (New York: Crown, 1978), 253-254.

of RNA processing for the expression of eukaryotic genes (pp. 33057-33062). Though risk assessment experiments were proposed at Falmouth, they have generally not been carried out, and, needless to say, the proposed revisions in containment levels for shotgun experiments are not based on their results. Many questions about the integrity of bacterial host-vector systems and the cloning of tumor viruses have been treated above. Here we discuss some of the unanswered questions about the expression of eukaryotic DNA sequences in bacteria.

In footnote 12 to the "Introduction and Overview" of the "Decision of the Director," Dr. Martin of NIH concludes that:

> (1) cloning of chromosomal DNA in E. coli DNA will pose little, if any, risk since the (RNA) maturation mechanisms have never been observed in prokaryotes; and (2) investigators who wish to develop prokaryotic cloning systems for the purpose of synthesizing useful biological products will utilize cDNA [complementary DNA] copies of functional mRNAs [messenger RNAs] or synthetic DNA with a nucleotide sequence derived from a known amino acid sequence as DNA inserts, (p. 33047).

However, § III-A-1 does not require that cDNA made from uncharacterized and unpurified eukaryotic message be cloned at a higher level of containment than the DNA from the same cells. Shotgun cloning of cDNA circumvents the barrier to functional expression presented by split genes and should be carried out at current levels of containment. Multicellular organisms which undergo development generally produce hormones which are powerful toxins if present at the wrong time in the organisms' life cycle. The possible inadvertent cloning of

a gene for such a protein is another reason for insisting on stringent containment of shotgun experiment in bacterial hosts or using uncrippled eukaryotic viral vectors when expression of genetic information is possible.

Dr. Martin's conclusion that the absence of mRNA maturation enzymes all but eliminates the risk of cloning eukaryotic DNA in bacteria can and should be tested. Several questions need to be answered:

(1) It is possible that not all eukaryotic genes -- particularly those for smaller proteins, peptides, and active RNAs -- contain introns (unexpressed DNA sequences in a eukaryotic gene). Genes without introns may not require processing for functional expression.

(2) Fragments of some proteins have been found to retain biological activity. Examples range from cytochrome b5 to the proteins coded for by the rII region of the T-even phages.[19/]

(3) If DNA sequences containing introns are expressed in bacteria in the absence of RNA processing, the (nonfunctional) proteins synthesized may have immunological cross-reactivity with their native relatives or with similar proteins in other species. The resulting bacteria may then be vectors for new autoimmune diseases.

The problem of autoimmune disease and recombinant DNA was discussed at the Falmouth conference by Dr. King. (F: 663-667).

19/ Stent, op. cit. and B. Hagihara et al., The Enzymes, P. D. Boyar, ed. (New York: Academic Press, 1975), pp. 550-594.

Examples of autoimmune conditions induced by bacterial or viral infection include rheumatic fever, acute glomerulonephritis, Goodpasture's disease, experimental allergic encephalomyelitis, and experimental antiglomerular basement membrane nephritis. Esquivel, Rose, and Kong have shown that purified mouse thyroglobulin combined with bacterial surface polysaccharides causes a potent autoimmune response when injected into mice.[20/]

Fragments of proteins can fold into native domains. This has been found to hold for large fragments such as the constant region of immunoglobulins and small fragments such as amino acids 53-69 of staphylococcal nuclease and a 17 residue disulfide loop in lysozyme.[21/]

An immune response to such domains may result in the production of antibodies which cross-react with vital indigenous proteins. The interactive nature of the immune response may make a protein which is a combination of native and novel domains a good breaker of immunological tolerance. This is especially true if the protein is presented in the context of a bacterial cell surface.

Thus, several testable questions remain to be answered before the risks inherent in shotgun experiments with eukaryotic DNA and cDNA are understood. Until these experiments are carried out and published in the scientific literature, the current containment levels should be maintained.

20/ P. S. Esquivel et al., Journal of Experimental Medicine, 145 (1977), 1250.

21/ M. Z. Attasi, et al., Biochimica et Biophysica Acta, 420 (1976), 358-375; M. Z. Attasi, et al., ibid., 427 (1976), 745-751; M. Z. Attasi, et al., Immunochemistry, 13 (1976), 7-14; M. Z. Attasi, et al., ibid., 13 (1976), 547-555; J. G. Curd, et al., Federation Proceedings, 34 (1975), 550.

VII. ADMINISTRATIVE DISCRETION AND DECENTRALIZATION

The same philosophy which has prompted the proposed reduction in containment levels is also the basis of the proposed increased reliance on Institutional Biosafety Committees (IBCs) and increased discretion for them and the Director of NIH. According to the Director, the lack of information about risks warrants looser administration of the guidelines.

> Two years' experience with the guidelines has offered valuable tutelage in the limits of external (Federal) control of laboratory experimentation ... Without a base [of information about risks], conventional regulation is difficult at best, and at worst can be preposterous. 43 FR at 33045.

Instead of "traditional regulation" NIH proposes a form of enforcement which institutionalizes conflict of interest and provides even less accountability for the Director of NIH and the IBCs than the previous guidelines.

Dr. Frederickson himself has recognized the problems of having NIH both promote and regulate recombinant research and recommended that new legislation relieve NIH of regulatory responsibility.[22/] There have already been two reported cases of violations of the 1976 guidelines. In both instances, laboratories of researchers connected with the formulation of the guidelines were involved. The NIH was unwilling to impose serious sanctions against the offending parties, thus

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22/ Recombinant DNA Research and Its Applications, Oversight Report by the Senate Subcommittee on Science, Technology, and Space, August 1978.

highlighting the disincentives in the current system of enforcement for researchers and IBCs to report accidents or violations.

These proposed revisions exacerbate the conflicts of interest inherent in self-regulation by shifting more of the responsibility for setting containment levels to IBCs which are even closer than NIH to the scientists with the greatest interest in pursuing the research. At the same time that the proposed revisions increase the conflict of interest problems they decrease the accountability of the Directors and the IBCs by allowing more discretionary case by case decisions -- i.e., exemptions, exceptions and lowering of containment levels.

This trend should be reversed by having the Office of the Secretary of Health, Education and Welfare assume more supervisory responsibility for the enforcement of the guidelines. This does not mean that HEW should become directly involved in regulation. However, in the absence of Federal legislation on R-DNA, HEW could make NIH and the IBCs more accountable by providing broad standards to define the limits of their discretion.

First such standards should define the circumstances under which the guidelines can be revised. In particular, the standards should require that changes in the guidelines be tied to the results of a risk assessment program. HEW should also provide that exceptions to the guidelines can only be granted when necessary for a risk assessment experiment and

define what constitutes a showing of necessity. Similarly, HEW should define what kind of showing must be made before an IBC can approve a lower containment level. Finally, HEW should establish a system for spot checking containment decisions made by NIH staff and the IBCs.

VIII. MEMBERSHIP AND ROLE OF THE IBCs

We recommend a number of changes in the composition and management of the Institutional Biosafety Committees:

(1) Section IV-A-2, which defines the membership of the IBC should further restrict conflict of interest by prohibiting members from having any direct involvement except as a laboratory worker, in recombinant DNA or closely related research. The proposed requirement that members have "expertise" in assessing the risks of recombinant research will favor the inclusion of members with an overriding interest in promoting the research.

(2) A biological safety officer should be retained by all institutions engaged in <u>any</u> kind of recombinant DNA work. § IV-A-3 stipulates that a biological safety officer shall be designated at institutions carrying out recombinant DNA research at the P3 and P4 levels of containment. This is inadequate, given the emphasis placed on good microbiological practice and the

seriousness of the experiments allowed at P2 containment levels in the proposed revised guidelines. § IV-A-3 as written will only result in increased institutional pressure to dergulate experiments to a level where a biological safety officer is not needed.

(3) The biological safety officer should be an exclusive full-time position. Under the proposed revisions, the biological safety officer need not be a new member of the institutional staff. Academic taboos and institutional hierarchies would reduce the effectiveness of the position if the person holding it has other institutional responsibilities.

(4) At least one member of the IBC should be a non-doctoral person from a laboratory technical staff. § IV-A-2 recommends this; we believe it should be a requirement.

(5) The local IBC should have the authority to <u>raise</u> as well as make single step reductions in the containment levels for some experiments with purified DNA and characterized clones containing recombinant DNA molecules. (§ IV-A-2-b). This may be appropriate at medical centers where a large number of hospital patients who would be especially susceptible to any breach of containment are in close proximity to the laboratories. Another case where a local IBC may want to set more

stringent containment levels is one in which a laboratory has previously been the site of an accident or violation of the guidelines or a laboratory whose members are consistently unable to implement safe microbiological practices.

IX. LABORATORY SAFETY AND PROCEDURES; SANCTIONS

We are distressed that NIH has not established a uniform and mandatory training course for laboratory workers and support personnel. We draw your attention to the recommendation of the US-EMBO Ascot workshop for viral DNA work with P2/EK 1 levels of containment: "It was emphasized that containment practices must include adequate training and the use of high quality microbiological technique." (42 F.R. at 33163). The present guidelines do not translate this recommendation into specific requirements, preferring instead to leave the matter unnecessarily vague. (§ II-A, p. 33071). Legislation regulating recombinant DNA activities which was recently passed in New York contains provisions for training workers involved in experiments at the P2, P3, and P4 levels of containment. Such a program should be established on the national level.

None of the physical containment levels prohibit people on antibiotic or immuno-suppressive drugs or people with open lacerations or chronic digestive abnormalities from entering the laboratories. The new guidelines appear to have deleted a provision of the September 27, 1977 proposed revised guidelines

which stipulate that "Individuals receiving antibiotics should not work with prokaryotic host-vestor systems during therapy nor for seven days after." (42 F.R. 49604). Since commonly used vectors are plasmids coding for antibiotic resistance, those workers undergoing antibiotic therapy would be good potential carriers for bacteria containing recombinant DNA. This has been well documented in animals and humans. For example, Timoney reported that 88% of 249 strains of S. tymphimurium isolated from diseased animals in New York State from 1973 to 1976 were resistant to six commonly used antibiotics. Ninety-one percent of these strains possessed transferrable resistance.23/ Dr. Levy reported at the Falmouth conference that resistant strains proliferate in farm inhabitants (including humans) upon incorporation of antibiotics into animal feeds. (F: 688-690) Resistant strains can be passed back and forth between animals and humans.24/ Dr. Levy concluded that:

> ... we must ... bear in mind that antibiotic usage is widespread and that the drugs themselves are major selective forces for resistant organisms. Thus, if a recombinant vector with a resistance marker were to escape into the environment, it would then have a better chance for survival, an undesirable feature. Therefore, antibiotic markers of commonly prescribed drugs should not be used on vectors for recombinant DNA research. (F: 690).

23/ J. F. Timoney, Journal of Infectious Diseases, 137 (1978), 67.

24/ S. B. Levy, Nature, 260 (1976), 40-42.

At the same meeting Dr. Curtiss noted:

> [T]he intestinal environment becomes much more conducive to conjugational plasmid transfer if an individual is receiving antimicrobial therapy. The pH, Eh (oxidation-reduction potential), and volatile fatty acid concentration then change to values more favorable to conjugational events. There is also a decrease in drug-sensitive normal flora; the resultant void is filled by the newly introduced strains and drug-resistant flora which possess conjugative plasmids. For these reasons, the NIH Guidelines for Recombinant DNA Research specify that individuals cannot conduct recombinant DNA research during, and for seven days following the cessation of, antimicrobial therapy. (F: 672).

We urge the NIH to reinstate the antibiotic provision of the September 27, 1977 proposed guidelines.

We recommend that NIH set up a rigorous epidemiological program to monitor and track all laboratory workers engaged in recombinant DNA research. The guidelines (§ IV-A-1-e) leave the question of surveillance at the discretion of the institution doing the research (p. 33084). NIH funding of recombinant research provides an opportunity to study potential risks. This opportunity to monitor the health of occupationally exposed laboratory personnel, and thereby collect data to evaluate these risks, should not be lost. Such an effort is a necessary element of any risk assessment program.

Finally, the sanctions provided for non-compliance with the guidelines (§ IV-D-1) are inadequate. By making the draconian measure of grant denial the only sanction, NIH creates a great disincentive to reporting and effective enforcement. Lesser sanctions should be provided so that violations will

not go unpunished as happened with the two reported violations of the 1976 guidelines. Such sanctions could include a fine imposed as a percentage reduction of the grant, removal of the principal investigator from the project, or NIH takeover of the functions of a poorly run IBC. IBCs should also be required to develop a plan for sanctions which the institution can and will impose.

CONCLUSIONS

The proposed reduction in containment requirements is not warranted by the scientific information now available on risks. A comprehensive assessment of risks must be completed before any such reduction is implemented.

The proposed administrative changes exacerbate the problems of self regulation. HEW should supervise administration and enforcement of the guidelines.

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DEPARTMENT OF BIOCHEMISTRY

PAUL BERG
Willson Professor of Biochemi

September 20, 1978

Dr. Donald Fredrickson, Director
National Institute of Health
Building 1, Room 124
Bethesda, Maryland 20014

Dear Don,

Your commentary and the proposed revisions of the Recombinant DNA Guidelines revealed how far we have moved since the issue of potential risks associated with recombinant DNA research was first raised publicly. In spite of the occasional ferocity, stridency and all too frequent politicalization of the discussions, features that turned me and others off to continuing involvement, you and your colleagues have persevered, steered a reasonable course while peppered with foolish and intemperate advice and arrived at proposals, which in the main are workable and a basis for further evaluation.

My estimate of the potential risks of recombinant DNA research and how to deal with them have certainly changed in the last few years. There is nothing remarkable or sinister about that; as scientists we are obliged, constantly, to reexamine and reinterpret our hypotheses, taking into account new developments, new data and fresh insights. The Asilomar Converence Report insisted repeatedly that the premises, conclusions and practices in the recombinant DNA field needed to be reviewed, reevaluated and updated continuously. Lest there be any misunderstanding about how I feel now let me say that I no longer have concerns about the safety of most recombinant DNA experimentation; consequently, it becomes increasingly difficult to justify to myself and others the amount of time and money being expended against risks that are highly improbable: perhaps more unlikely than the probability that space vehicles reentering our atmosphere will fall in populated areas (a possibility which elicited little concern or comment from the media or public spirited citizens) or any one of hundreds of other potentially calamitous but routine activities and practices. I could be mistaken in my estimate of the risks but I don't believe so. However, being fallible, I have supported the NIH's efforts to devise sensible and workable guidelines to minimize the possibility of any risk. I can continue to do so as long as they do not become unnecessarily restrictive and stifling to research progress

and creativity. Unfortunately, some portions of The Guidelines, but particularly the implementation of The Guidelines, are already having that effect. I urge you to be on guard against that outcome.

I have from time to time reflected on my participation in raising the recombinant DNA issue in 1974. Considering what we knew then and what we perceived as the risks, I don't see how I or any of us could have done otherwise. Had we been privy to the information, discussions and experience available today, that action would surely not have been taken. Opponents of recombinant DNA research, or those wishing to restrict its applications, can no longer cite that document as an expression of present day concerns.

There are several specific comments about PRG-NIH that I want to register; hopefully they will be helpful to you in arriving at the final form of this version of The Guidelines.

1. Your decision to remove a large number of innocuous experiments from the purview of The Guidelines is a wise one; such experiments have never been the subject of concern even amongst those who opposed the research. I am also in general agreement with the reduction in containment requirements for most experiments using the EK host-vector systems. The large body of experience gained during the past four years and the advice of infectious disease experts, epidemiologists and evolutionists suggests that the earlier concerns were unwarranted.

2. Earlier I had suggested that PRG-RAC's recommendations for experimentation with recombinants containing animal or plant virus DNAs needed to be reevaluated. The present recommendations, drawn from the US-EMBO workshop and review committee's reports, are more realistic, reflecting a different assessment of the risk-benefit equation than was made four years ago. This line of experimentation should lead to important advances in understanding viral genome structure and function. In my view the potential benefits of permitting these experiments to proceed as now recommended far outweigh the hypothetical and rather unlikely risks; consequently, I support the recommendations in Section III-A-2.

3. As I am involved in such research I'd like to comment at greater length on the containment requirements for experiments using animal virus vectors for cloning in mammalian cells (Section-C).

a) Infection of non-permissive cells results in a non-productive infection, but non-productive infections may also result from infection of <u>permissive cells</u> e.g. when

permissive cells are infected with mutant genomes which can not complete the infectious cycle. I foresee the development of eukaryote plasmids constructed from portions of Polyoma or SV40 DNA that can propagate in permissive mammalian cells without killing the cells or producing progeny virus. That contingency is obscured by using the words non-permissive cells in connection with non-productive infections.

b) I am totally confused by the wording or intent of paragraphs III-C-1-a-(1)-(b and c) dealing with polyoma vectors particularly when they are compared with the analagous instructions for the SV40 DNA vectors in paragraph III-C-1-b-(1)-(b). The word defective and intact are not appropriate. How can one use an intact polyoma DNA as a vector? If an exogenous DNA sequent is introduced into the polyoma DNA it is no longer intact; moreover, the introduction of foreign DNA into the polyoma DNA will render it defective because it will inactivate an essential function or enlarge the DNA to a size that prevents its encapsidation-hence it becomes defective as a potential virus. I think The Guidelines want to distinguish between the cases where a recombinant is defective, therefore requiring a helper, and the very rare case where a recombinant is non-defective and does not need a helper for multiplication. The operational definitions that define the containment requirements should be whether the propagation of the recombinant is helper-dependent or independent.

c) In assigning P2 containment to experiments in which african green monkey cell DNA is propagated with SV40 DNA vectors, were human and rhesus monkey cell DNA to be excluded from this category? Human and some other primate cells do support SV40 multiplication and, therefore, presumably cell-virus DNA recombination does occur naturally; shouldn't paragraph III-C-1-b-(a)-(2) read "uninfected primate cells in which SV40 is known to multiply"? I am also puzzled by the logic which permits P2 containment for propagating monkey DNA in SV40 vectors but retains a P3 containment requirement for propagating recombinants with yeast, Drosophila or rabbit DNA (compare paragrahs III-C-1-b-(1)-(a)-(2) and III-C-1-b-(1)-(b).

4. Another point which needs further consideration is the continued use and definition of the words "purified" and "vigorously characterized" (see paragraph III-A). In as much as I drafted the wording to explain the terms appearing in footnote 38 and 40 of Section V at the RAC meeting in La Jolla in December 1975, I know that its adoption reflected

the supercautious mood prevalent at that time rather than a clear-cut scientific judgement. In my view requiring that a DNA fragment should be 90-95% pure (as judged by at least two different analytical procedures) to remove it from the "shotgun" classification is more realistic and no less safe. Requiring that a DNA fragment be >99% pure prior to cloning asks for the most stringent and detailed documentation without any real advantage. For example, if prokaryote or mouse DNA, can be "shotgunned" into polyoma vectors under P2 conditions, I do not understand why segments of DNA from eukaryotes e.g. or gamisms that do not produce potent polypeptide toxins as exemplified by yeast, Drosophila or even rabbit, need be >99% pure prior to cloning in polyoma! What is the concern if they were 50, 90 or 95% pure?

In the paragraphs of Section III-A-2, dealing with cloning various virus DNA and cDNA sequences, the word purified appears throughout without referencing to footnote 38 or 40. Does purified in each of these cases mean >99%? If so, is that intentional or inadvertent? In my view if a particular segment was 90-95% pure that would be sufficient since the isolation and screening of only 20 to 50 clones would insure the recovery of the desired recombinant with little or no increased risk. Even with DNA segments that are 50% pure half the clones would be the desired ones. In short by recommending that segments be greater than 90% pure only a small number of clones need to be isolated and examined, thereby, drastically reducing the probability of creating or releasing unexpected recombinants to a vanishingly small number.

5. I am particularly unhappy about the recommendations PRG-NIH proposes regarding the development, review and certification of new HV systems. The breakthrough with yeast transformation and the ability to propagate exogenous DNAs in S. cerevesiae has very important ramifications in extending the recombinant DNA technique for basic and applied purposes. Yet ORDA and RAC are confounding and, I believe obstructing these developments. Long delays in coming to a conclusion are particularly frustrating. I suggest that as such scientific problems arise ad hoc committees, composed of knowledgeable and responsible scientists in the relevant disciplines, should be convened as quickly as possible to examine the issues and advise RAC on possible courses of action. The U.S.-EMBO workshop and report is a model of how this can be done. In this way actions on several important issues could be proceeding in parallel rather in series. Such committees or workshops should already be at work trying to assess the possible risks, if any, of cloning foreign DNAs in yeast and in B. subtilus. As it now stands no decision is tantamount to a ban on these experiments. Can we really defend or condone banning the introduction of Drosophila or mammalian DNAs into S. cervesiae? Even with the uncertainties that existed at Asilomar cloning such DNAs in E. coli K12 was not forbidden. While the inquiries are proceeding there should be recommendations of interim physical containment and specified biological properties to permit such experiments to proceed. Investigators would be informed

that such recommendations are tentative and will be modified as new information becomes available. This would permit investigators to explore the feasibility of such experiments and lay the groundwork for settling on the final containment requirements of such experiments. As matters now stand the absence of a policy is tantamount to a ban on such experiments.

6. There are also several comments and concerns about the procedures set forth in PRG-NIH.

a) I support enthusiastically the change that permits local IBC's to approve proposals and the investigator to initiate the experiments after obtaining such approval. The previous procedures were cumbersome, time-consuming and unnecessary. In my view the greatest risk to non-compliance with The Guidelines is for investigators to be confronted with an unresponsive, time-wasting bureaucracy. I have been impressed with how efficiently and unobtrusively (for the institutions and investigators) the procedures for safe-handing of radio-isotopes are administered. Hopefully surveillance of recombinant DNA research can be made as routine as the procedures used for experimentation with radio isotopes.

b) As a member of an IBC I am particularly sensitive to the workload imposed on that body by the Recombinant DNA Guidelines. I am sure you are cognizant of the monetary costs in faculty and staff time needed to enforce them. Presumably, this gets charged to indirect costs, thereby making the costs of research to all granting agencies still higher. I hesitate to inquire what the costs of IBC time have been to Stanford during the past year. I suspect that these costs together with those attributable to your interminable involvement in these matters introduces a further and substantial drain on an already shrinking NIH research budget.

c) I note that the PRG-NIH requires that all, not just NIH funded, recombinant DNA research at institutions receiving NIH support must comply with The Guidelines. But the instructions for how non-NIH funded research is to be reviewed, reported, monitored etc. are not clear enough. My deductions from reading Section IV A-D in Appendix C (particularly paragraphs IV D 1-10) are that a non-NIH funded project must be reviewed, approved and reported as is done for NIH-supported research. Since formal approval is no longer needed prior to initiating the work, what is the difference between the two procedures? Why couldn't the instructions read, that all recombinant DNA research, regardless of its funding source but carried out in an institution receiving NIH funds, must be treated as if the research is NIH-funded? In that way

one procedure would do for all? It would greatly ease the burden of the IBC's to treat all recombinant DNA projects alike.

7. I seriously question the necessity for public discussions and review of each and every subsequent modification in the Guidelines and its Appendices. I believe the process is already public enough in as much as the Director's Advisory Committee and RAC have public members and meet in full public view, only after public announcement of the meeting's time and place; changes in the Guidelines are made in close consultation with these groups and final decisions are published in the Federal Register and Recombinant DNA Bulletin. Must every technical decision be the subject of the same interminable review process now in progress? I was struck by the number of places in PRG-NIH where the Director is required to provide "appropriate notice and opportunity for public comment" prior to making or implementing decisions. I believe a distinction should be made between purely technical and scientific matters and broader policy issues that frequently elicit political, ethical, religious and other considerations.

8. The phrase "case by case" review occurs frequently in PRG-NIH, particularly where construction of recombinants involving two different viral DNAs is considered. But I found nothing more than general statements about how such case by case review would be conducted. May I suggest that an ad hoc committee or subcommittee of RAC formulate a plan for how such reviews will be conducted e.g., by whom (ORDA or RAC?), when (on demand or periodically), what constitutes a decision and who makes it (the Director, ORDA or RAC?) etc. Will such decisions also require public review and comment? That group could also construct a list of putative high, intermediate - and low-risk combinations to guide investigators now planning such experiments. For example, there is considerable interest for introducing the thymidine kinase gene from herpes simplex virus into either SV40 or polyoma DNA vectors; this is quite a straight-forward almost trivially simple, but nevertheless important experiment; yet, presently it is a forbidden experiment and unless the case by case reviews are expedited it will remain forbidden.

I had not intended to write at such length but my justification for doing so is that you might find my comments useful in your deliberations.

This summer as I sat through two Gordon Conferences reviewing the recent advances using the recombinant DNA methods I wished that you were there. I particularly wanted you to see and experience, first hand, the dynamism, excitement and explosive progress that these developments have engendered. The recombinant DNA methodology and rapid nucleic acid sequencing

techniques have revolutionized molecular biology and genetic chemistry; the ignorance and confusions that obscure and delay solutions to important biomedical problems are being blown aside. I am more than ever confident that we, you, I and the many others who have had a hand in initiating and supporting recombinant DNA research, will live to see its fruits harvested.

With sincere best wishes for continued success,

Sincerely,

Paul

Paul Berg

PB:vs

BROWN UNIVERSITY Providence, Rhode Island • 02912

Division of Biology and Medicine

September 20, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson,

I would like to comment on Section II-B-3C(5) of the proposed revised guidelines for recombinant DNA research: "Laboratory doors shall be self-closing."

We were in the final stages of constructing a P3 facility when the proposed revised guidelines came out. We had designed the facility to use sliding doors on the grounds that swinging doors would produce an undesirable pumping action. The proposed requirement that doors be self-closing now presents considerable difficulties, however.

Whereas it is relatively easy and inexpensive to make a swinging door self-closing, this is not the case for sliding doors. After looking into the matter at some length, we have found that the only workable solution is to make the sliding doors completely automatic, i.e., electrically operated. Unfortunately, this is rather expensive. We have estimates that start at $1500-2000 per door, and we are not sure that this reflects the final overall cost.

Since sliding doors do seem to offer some advantages over swinging doors, I would like to suggest that the guidelines be worded in such a way as to make facility design compatible with either sliding or swinging doors.

I would suggest that the guidelines deal with the intent of closed doors as a practice rather than a facility requirement. Of all the practices that are required of workers in a P3 facility, that of keeping the door closed is the most easily monitored and the least demanding. Thus it does not seem absolutely necessary to require that this aspect of P3 work be fully automated.

I suspect that our local biohazards committee may ask for a "ruling" on this question from you. I know you are probably swamped with such requests, but it would be extremely helpful to us if we could have a reply or "official opinion" as this is the only matter that stands in the way of having our laboratory certified.

Thanking you for your consideration of this matter, I am

Respectfully yours,

Arthur Landy

Arthur Landy
Professor of Medical Science

AL:mm

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September 20, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20016

Dear Dr. Fredrickson:

I have read the proposed Revised Guidelines for Recombinant DNA Research and would like to express my approval of them. I must say that when the original guidelines came out I was skeptical of claims by many that recombinant DNA research posed no hazard. In light of more recent findings concerning the feebleness of E. coli K12 and particularly regarding the structure of eukaryotic genes, my earlier misgivings have largely been allayed. While I believe that some precautions are still necessary, these do appear to be amply embodied in the proposed revision, and I fully agree with the general relaxing of standards. My own work with recombinant DNA involves E. coli genes cloned into E. coli, a system which worries nobody to my knowledge; I believe that removing this and similar systems from being covered by the Guidelines is a realistic step and will do much to foster credibility within the scientific community.

Sincerely yours,

John Little, Ph.D.
Adjunct Assistant Professor

JL:kb

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September 21, 1978

Director
National Institutes of Health
Bethesda, Maryland 20014

Subject: Proposed Revised Guidelines, Recombinant DNA Reasearch

Reference: Federal Register 43, 146 (July 28) 1978

Dear Dr. Fredrickson:

We have reviewed the proposed revised guidelines for Recombinant DNA Research as published in the Federal Register. While the document is generally very excellent, we believe there are some points which require amplification. They are as follows:

A. Add to paragraph II-B-2-b, II-B-4-b-(1) and II-B-4-b-(2) the following statement: "Biological Safety Cabinets shall be certified in situ upon installation, if moved or relocated, and at least annually". Add to paragraph II-B-3-b and II-B-4-b-(3) the following statement: "Biological Safety Cabinets shall be certified in situ upon installation, if moved or relocated, and at least annually and preferably semi-annually".

Many users are unaware of the need for certification of new units in situ, and believe that the manufacturer's factory certification is adequate. While section IIIB of the Laboratory Safety Monograph (P130, second paragraph) states that cabinets should be certified under the conditions noted above, the statement is not a requirement, and the Monograph is considered a "supplement to" rather than a part of the guidelines and has no regulatory impact. We have had the experience that investigators working with recombinant DNA have refused to have their cabinets recertified annually because the guidelines did not require it (reference our letter to Dr. Gartland of July 6, 1978).

Adding the above statements makes it clear that periodic certification is required.

We are recommending semi-annual certification for cabinets in P3 laboratories (and moderate risk and clinical laboratories working with class 3 agents) because we have found that many Biological safety Cabinets can increase in pressure drop by 50% or more in a 6 month period of heavy use. NSF Std 49 permits a decrease in airflow of up to 10% as a result of a 50% increase in pressure drop. Thus, over the course of a year, a loss of airflow of 20% or more could occur. We understand that Dr. Barkley has data showing that a 20% loss in airflow results in one order of magnitude decrease in containment. At P3 level, we think this is sufficient reason to warrant twice annual inspections. At P4 level, the exhaust systems of class III cabinets are typically adequate for once annual certification, and class 1 and class 2 cabinets in suit rooms are adequate if certified once annually, but class 1 or 2 cabinets used with HV2 Biological Containment in the absence of a suit room should be certified twice annually for the reasons noted above.

B. We have a number of comments to paragraph II-B-3-c-(7) and are splitting them up for ease of description and clarity. The first suggestion is to add after the second sentence "The system shall contain an alarm which will operate if loss of directional airflow occurs and shall preferably be interlocked to cut off any incoming air if loss of directional airflow occurs." The directional airflow property of the P3 laboratory is an important containment feature. We have seen a number of system failures which would have caused reversal of the airflow direction in systems without interlocks.

C. The end of paragraph II-B-3-c-(7) of the proposed guidelines states, "The exhaust air from the (P3) laboratory shall be discharged to the outdoors so that it is dispersed clear of occupied buildings and air intakes. The exhaust air from the laboratory can be discharged to the outdoors without filtration or other treatment." This is a change from the 1976 guidelines. We propose that this part of paragraph be rewritten as follows:

"The exhaust air from the (P3) laboratory shall be either HEPA filtered and discharged outdoors or shall be discharged to the outdoors so that it is dispersed clear of occupied buildings and air intakes in which case it need not be filtered or otherwise treated."

We believe that this revision, in conjunction with comments below, will clarify the guidelines and avoid some possible legal

problems. There are a number of facilities which utilize HEPA filters in the exhaust system because there is some question as to whether the exhaust air is dispersed free of all buildings and intakes. We know of at least six in service or in construction, some of which have been approved by NIH. Our proposed revision makes it clear the HEPA filter approach is acceptable whereas the PRG-NIH as presently written does not permit this approach. As may be seen from our comments below, an alternate to "dispersed free of buildings and intakes" is essential in many cases.

D. The phrase "dispersed clear of occupied buildings and air intakes" in paragraph II-B-3-c-(7) needs better definition. Placing exhaust stacks on a roof and exhausting upward at velocities above 2,500 feet/minute as stated on page 148 of the Laboratory Safety Monograph doesn't always work. We recently participated in a test of a facility contained in a U-shaped building with a dormitory building closing off most of theopening of the U. The building roof is approximately 70 feet from the ground. The exhaust stack is 30 feet high. The wind was blowing NNE at about 10-15 knots. The exhaust velocity from the stack is about 2,300 feet/minute. When a smoke bomb was ignited in the exhaust stack a visible fraction of the smoke (perhaps 1%) was drawn down into the courtyard between the laboratory and the dormitory. Smoke could be seen 10 minutes after the test at a level equal to second story dormitory windows. This facility has HEPA filters in the exhaust system so we do not feel that the incomplete dispersion represents a health hazard. We do feel it illustrates the problem in determining whether adequate dispersion is obtained.

We propose that a section be added to the guidelines defining a procedure for determining adequacy of exhaust dispersion. A suggested definition of adequate dispersal is "Not more than 1 part of exhaust air in 10^6 parts of air shall impinge upon any occupied building or air intake." This should be determined by wind tunnel tests simulating a range of wind speeds at each of a number of wind directions covering the entire compass at intervals of $22\frac{1}{2}^{\circ}$. Wind tunnel tests are required because wind speeds and directions are not so predictable and cooperative as to permit tests on the actual facility.

The need for wind tunnel tests could be waived under a particular set of circumstances which we believe will provide adequate dispersion. All are required.

1. The exhaust stack shall have a height of at least 60%

of the height of the building and an exhaust velocity upwards of at least 2,500 fpm.

2. There shall be no taller buildings, hospitals, or densely populated areas within a ¼ mile radius.

As a practical matter, the above recommendations are tantamount to a recommendation that the exhaust air be HEPA filtered in almost all cases. The question will undoubtedly be asked, "Is this necessary?".

Experience with clinical microbiology laboratories in hospitals, most of which do not approach the P3 guidelines, suggests that the spread of infection from laboratory ventilation systems is nil. On the other hand, these laboratories generally deal with class 3 agents that are not highly contagious (do not cause epidemics) such as M. Tuberculosis, and whose etiology is well known. The purpose of P3 containment as we understand it, is to reduce the probability of escape and replication of a viable organism containing recombinant DNA to a very small number. Levels of escape which are acceptable for organisms such as M. Tuberculosis are not acceptable for organisms from a P3 laboratory. We therefore conclude that the above recommendations are indeed necessary.

E. Section III-B-5 of the Laboratory Safety Monograph specifies a leak test procedure for positive pressure plenums in Class II Type A cabinets. We have two comments relating to this paragraph

1. We understand that NIH does not use this procedure for Class II cabinets in Bethesda, but uses instead a pressure test specified by Test Protocol No. 16 to RFP 263-76P(62)-0125cc. We recommend that this protocol be listed as an alternate procedure.

2. We have found that pressure plenums on Class II cabinets can be tested using DOP. The procedure is similar to paragraph III-B-7 of the Monograph except that gaskets and joints outside the cabinet are scanned. Without turning on the DOP, these areas are scanned to determine a background reading. Then the DOP is turned on and the scanning repeated. An increase reading of .01% or more indicates a leak. The procedure is applicable in any laboratory where the background reading does not exceed .1% (less than 1% of the laboratories we test have reading above this value). A linear photometer is required. This procedure is simpler than the Halogen test, eliminates the release of fluorocarbons into the atmosphere, and is consistent with the test requirements for the exhaust HEPA filter. We suggest that this procedure be added to the Laboratory Safety Monograph.

F. The Laboratory Safety Monograph does not contain a Leak Tightness test for Class II Type B cabinets. In order to perform the HEPA filter leak test in this cabinet, the bottom access panels must be removed. If they are not reinstalled leak tight, unfiltered ambient air will be drawn in through the leaks and will reach the work surface of the cabinet without filtration. Therefore a leak test is required. The procedure of pressurizing and soap bubble testing is sufficient.

G. We would like to see a recommendation for the use of a separate centrifuge room or cubicle added to section IV-A of the Laboratory Safety Monograph. The room should be designed so that the ventilation system can be sealed off from the rest of the P3 facility so that the room can be decontaminated with paraformaldehyde without shutting down the rest of the facility or losing the inward airflow to the facility. Rotor failures in ultracentrifuges are common and provision should be made for containing the spill and decontaminating the area when a failure occurs.

H. Paragraphs III-B-7-b-(3) and III-B-7-b-(5)-(a) of the Laboratory Safety Monographs are written around a particular Laskin nozzle containing 2 shearing jets (these numbers are also used in NIH specifications and NSF Std 49). The original work on DOP generators used a 4 jet nozzle (Echols, W.H. and J.A.Young, "Studies of Portable Air-Operated Aerosol Generators", NRL Report 5929, U.S. Naval Research Laboratory, Washington, D.C. July 26, 1963). This nozzle is currently sold by one manufacturer. It requires 2 scfm of air and produces twice the smoke that a 2 jet nozzle produces. These paragraphs should be revised to permit the use of this nozzle on a basis of 1 per 1,000 cfm. This recommendation is also included as part of the comments below.

I. The integrity of the containment systems depends heavily on the adequacy of the certification procedures used, and particularly the equipment used to leak test HEPA filters and measure airflow. The Laboratory Safety Monograph does not adequately define equipment and calibration requirements. Enclosed is a paper "Testing of Laminar Flow Equipment" Journal of the Parenteral Drug Association 32:174-181 (July-Aug) 1978 which discusses some of the problems involved in making sure test equipment is correct for certification. We suggest that the paper be included as a reference in section VI-F of the Laboratory Safety Monograph, and that the data of figures 1,2,4 and 11 be added to appropriate parts of section III-B of the Monograph. When inserting this data in the monograph, the sampling probe

diameter (figure 4 item 5 and figure 11 item 6) should be reduced to 3/4" since some Class II cabinets have exhaust velocities over 250 feet/minute. We believe these additions are necessary because we have seen equipment and procedures in the field which fail to conform to almost every specification that we have recommended.

The above comments are submitted in the hope that their inclusion will advance both research and safety simultaneously. If there are any questions about any of our points or if further elaboration is desired, please contact the undersigned.

Very truly yours,

MEDICAL REPAIR LABORATORIES INC.

Robert I. Gross
President

RIG:fw
Encl.

The Ohio State University

Graduate School
University Hall
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21 September 1978

Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

We wish to respond to proposed revised guidelines for recombinant DNA research as published in the Federal Register, Vol. 43, No. 146, July 28, 1978.

The proposed revised guidelines are viewed on this campus as a reasonable relaxation of current guidelines brought about by the failure to demonstrate the hazards that have been improperly attributed to experiments involving recombinant DNA. Tangible results will be felt at The Ohio State University should the proposed revision advance to final promulgation. Several experiments now conducted at lower levels of containment will be exempt from guidelines, and the containment level for one project will drop from P3 to P2. Thus, for at least one group of researchers, the requirements for regulation and monitoring would decline and no new facilities would be needed to conduct any of the research they propose with recombinant DNA. We applaud NIH for its continuing evaluation of the need for the close surveillance affiliated with recombinant DNA research and urge on-going consideration for further reductions in regulation and containment levels.

While we accept the need for NIH to maintain a registry of NIH-supported recombinant DNA research via the filing of Memoranda of Understanding and Agreement (MUA), we question the need to extend the registration process to non-NIH projects, especially at the P1 and P2 level. It is not clear that there need be the kind of monitoring of recombinant DNA research at lower hazard levels that would include the submission of a non-NIH MUA to NIH, review by ORDA and follow-up with the submitting institution should a protocol for non-NIH supported activities not conform to standards contained in the proposed revised guidelines.

A more acceptable approach would be to develop an institutional assurance program, of the kind used by DHEW for research involving human subjects, one component of which would be that institutions qualifying for a "general RDNA assurance" would review, administer and monitor all research involving recombinant DNA according to NIH standards articulated in the proposed revised guidelines. MUA's would be forwarded to NIH for federally funded projects and perhaps for activities at the P4 containment level supported by non-federal sponsors. Records of Institutional Biosafety Committees (IBC) would be available for periodic inspection by NIH as a method for insuring IBC compliance with terms of general RDNA assurances. Institutions unwilling or unable to qualify for general assurances would be required to submit information to NIH for all research activities involving recombinant DNA as described in the proposed revised guidelines.

One other provision of Section IV requires clarification. Paragraph IV-A-4-g, as written, permits the investigator to petition NIH, after notifying the IBC, for exceptions or exemptions to the proposed guidelines. While paragraph IV-A-4 implies that such petitioning would be done on behalf of the institution, it is possible that an investigator might seek exception or exemption against the wishes of the IBC, simply notifying the committee that he will take such action. Potential differences in interpretation of paragraph IV-A-4-g could be avoided by revising the paragraph to read "Petitioning NIH, after receiving the approval of the IBC, for exceptions or exemptions to these guidelines."

We appreciate the opportunity to respond to the proposed revisions of guidelines governing research with recombinant DNA and hope our comments will be given consideration.

Sincerely,

Jules B. LaPidus
Vice Provost and Dean

JBL:lfr
cc: Donald T. Witiak, Chairman
Institutional Biohazards Committee

TELEPHONE (313) 769-2858

SUSAN WRIGHT
1517 SHADFORD ROAD
ANN ARBOR, MICHIGAN 48104

September 21, 1978

Dr. Donald S. Fredrickson
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

I do not think that the general direction of proposed revisions to the NIH guidelines for recombinant DNA research is justified. The primary defense of these revisions, as reflected in your introduction to them, has been that there is now evidence which shows that the risks from recombinant DNA activities are less than was originally thought to be the case. Yet analysis of this evidence shows that there are many questions concerning its validity. Specifically: 1) The Falmouth conference reached consensus on a single point, namely, the improbability of converting the K-12 strain of E.coli into an epidemic pathogen. The possibilities of converting E.coli into a non-epidemic pathogen or of transfer of foreign genes to other strains were not ruled out. Indeed, NIH is funding a variety of risk assessment experiments to try to answer questions that were raised at Falmouth about the survival potential of E.coli K-12 and the probability of transfer. The proposed revisions are based on the assumption that the transfer experiments will yield negative results. As one commentator noted in testimony at the hearing, this is not only bad science: it is also bad administration. 2) The Ascot meeting on the risks of use of virus DNA was held in private: not even members of the British GMAG let alone scientists in the U.S. who have felt that a more conservative recombinant DNA policy was desirable were invited. The results of the Ascot meeting and the Bethesda meeting which followed it have not been published or discussed in open scientific meetings. It is therefore impossible to judge the validity of the conclusions that were reached. (Certainly it seems unlikely that members of the Ascot meeting would have approved the further whittling-down of containment levels that occurred at the Bethesda meeting.) 3) The argument that because no harm has occurred, recombinant DNA activities are safe involves a triple fallacy: a) since workers are not being monitored, we actually do not know what the effects of work with recombinant DNA are. b) If effects of recombinant DNA activities have a long latency period, they would not have been detected by this time. c) As several witnesses at the hearing pointed out, the argument confuses the ability to safely perform a process with the intrinsic hazard of the process itself. We surely would not want to have such arguments used in defense of removal of safeguards from nuclear power plants or from work on Q-fever.

While valuable protection might be lost by relaxing the guidelines, nothing would seem to be gained by doing so. As Norton Zinder pointed out in his testimony:

> The great promise of research with recombinant DNA has been and continues to be fulfilled. Numerous significant advances in our knowledge of basic biology have been made. Sooner than we had any right to expect the work will yield useful products. The current literature abounds with its success.

In short, recombinant DNA research is thriving. Why remove controls before consensus in the scientific community has been reached and before the results of the NIH-sponsored program of risk assessment are in?

In addition to results from the risk assessment program, there are at least two pieces of information that are likely to affect perceptions of recombinant DNA risks in the near future. First, there will be results from the Rowe and Martin experiement with polyoma virus DNA (To be published this fall). Second, there will be the independent analysis being conducted by Dr. Sydney Brenner of the MRC Laboratory for Molecular Biology, Cambridge, U.K. Dr. Brenner, as you know, was a member of the original Berg commitee and has consulted with the RAC. In a personal communication, he writes: "I now feel that the whole method of risk assessment used up to now is fragmentary, if not wrong, and that what is needed is a more systematic approach which I have tried to make." (September 12, 1978.).

Surely the rational approach is to wait, and to see what further risk assessment experiments and analysis produces and to make policy decisions on that basis. Rushing the revisions through this fall seems entirely unjustified.

Finally, I would like to endorse the position statement of the Coalition for Responsible Genetic Research on revisions. The Coalition feels that the proposed incremental changes in the present elite decision-making structures are inadequate. It also needs emphasis that "consultation," i.e., the provision of testimony at public hearings, is a quite different matter from sharing in actual decisions. Structural and procedural changes are badly needed to make possible full participation in decision-making by representatives of labor, environmental and consumer advocacy groups, public health officials, and government agencies with potential regulatory responsibility for recombinant DNA activities. Only in this way can there be confidence that public policy decisions for recombinant DNA technology are in the public interest.

Sincerely,

Susan Wright

Susan Wright, Ph.D.
Member, Executive Committee
Coalition for Responsible Genetic
Research.

SW/mks

The American Society of Plant Physiologists

Office of the President

September 21, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20014

Dear Dr. Fredrickson:

The Recombinant DNA Committee of this Society has prepared the enclosed comments and suggestions for revision of the guidelines for recombinant DNA research as they apply to potential uses in higher plants. I strongly urge you to consider these recommendations.

Sincerely yours,

Israel Zelitch

Israel Zelitch
President

Head, Department of Biochemistry
Connecticut Agricultural Experiment Station
P.O. Box 1106: 123 Huntington Street
New Haven, CT 06504

Enclosure

IZ:ehm

Report by Recombinant DNA Committee

AMERICAN SOCIETY OF PLANT PHYSIOLOGISTS

The proposed revised guidelines for recombinant DNA research (Federal Register Friday August 28, 1978) contain appropriate provisions for many important experiments. However, the situation in regard to experiments involving plant DNA has still not been as extensively considered as one might wish. Relatively few plant scientists are in a position to use recombinant DNA techniques, but the potential benefits to mankind from plant genome modification are as great as are those from animal genome modification. For example, the enhancement of seed protein quantity, quality, and of photosynthetic efficiency, is highly desirable as is also the widely-considered potential for genetic engineering of crop plants to enable non-legumes to fix atmospheric nitrogen.

Although the use of DNA viruses in plants is considered in the proposed guidelines (pg. 33081), the use of the Ti plasmid of Agrobacterium tumefaciens (crown gall) received scant attention. This is unfortunate since it probably represents the most useful potential vector for genetic engineering in plants.

Under the proposed guidelines (pg. 33089) insertion of DNA from E. coli and several other prokaryotes into Ti plasmid is permitted without restriction, but no insertion of eukaryotic DNA is allowed. The only basis for such a differentiation would be an ability for the Ti plasmid to conjugate with E. coli or other microorganisms. Deletions Tra^- in the Ti plasmid are available (J. Schell, personal comm. to J.D. Kemp) that render it non-conjugative. Hence, we believe that the Agrobacterium-Ti plasmid host-vector system is entirely safe for cloning plant DNA. Section III-B of the proposed guidelines (pg. 33080) provides the mechanism for obtaining approval for prokaryotic cloning systems. We recommend that all Agrobacterium-Ti plasmid combinations with a Tra^- deletion be quickly approved as HV1 systems.

Because of the importance of evaluating the possibilities for genetic engineering of crop plants, we think it important to include directions for the use of the Ti plasmid of Agrobacterium tumefaciens in the revised guidelines. In consultation with Dr. Kemp (Plant Pathology Department, Univeristy of Wisconsin, Madison) we have developed the following suggestion for the use of crown gall as a host-vector system. Since there is no evidence for the transmission of axenic plant tumors induced by Agrobacterium tumefaciens, crown gall is a safe host-vector system for eukaryotic recombinant DNA studies. Therefore, we recommend that the following underlined parenthetical phrase and the underlined sentence be inserted in Section III-C-4 (pg. 33084):

III-C-4. Plant Host-Vector Systems Other Than Viruses.

Organelle, plasmid (including Agrobacterium Ti plasmids), and chromosomal DNA's may be used as vectors. DNA recombinants formed between such vectors and host DNA, when propagated only in that host (or closely related strain of the same species), are exempt from these Guidelines (see section I-E). DNA recombinants formed between such vectors and DNA from cells other than the host species require P2 physical containment. Inoculation of hosts with HV1 approved Agrobacterium containing the DNA recombinants requires P2 physical containment. The development and .....

Timothy C. Hall, Department of Horticulture
University of Wisconsin (Chairman)

Joseph C. Polacco, Department of Genetics
Conn. Agricultural Experiment Station,
New Haven

FRIENDS OF THE EARTH 72 JANE STREET • NEW YORK, NEW YORK 10014 • (212) 675-5911

September 21, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Enclosed is my comment and recommendations on the proposed revisions to the recombinant DNA research guidelines which, in addition to the comment of Ms. Pamela Lippe, is submitted on behalf of Friends of the Earth.

Sincerely yours,

Richard M. Hartzman

Richard M. Hartzman

jc

enc

RICHARD M. HARTZMAN
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September 21, 1978

Mr. F. Peter Libassi, Esq.
General Counsel
Department of Health, Education and Welfare
Hubert H. Humphrey Building
Washington, D.C.

Dear Mr. Libassi:

As you requested at last Friday's hearing on the recombinant DNA guidelines, I am sending you my comments and recommendations on the proposed revisions.

While the enclosed document details my comment and recommendations, I would just like to indicate here the great concern of Friends of the Earth that provisions for NEPA compliance, for public participation, and for risk assessment be written into the recombinant DNA guidelines themselves. Vague discussions of these matters in supporting documents which have no force of law give us no assurance of their proper fulfillment.

With respect to NEPA, agreement on appropriate compliance for the proposed revisions and for future actions concerning DNA activities could constitute the basis for a settlement of the pending Friends of the Earth lawsuit. This is a serious problem on which discussions should be initiated in order to move toward resolution. I am willing to meet with you to pursue this matter further.

My sense at the hearing on Friday was that it would be extremely difficult to reach a final decision on the revisions without having further proceedings. Perhaps some informal group meetings could be arranged and possibly there could be an opportunity for reply comment.

I would like to compliment you for the evenhandedness with which you conducted the hearing.

Very truly yours,

Richard M. Hartzman

Richard M. Hartzman

jc

cc: Dr. Donald S. Fredrickson
Dr. Julius Richmond
Dr. Henry Aaron

enc

COMMENT AND RECOMMENDATIONS OF RICHARD M. HARTZMAN ON THE PROPOSED REVISED NIH GUIDELINES ON RECOMBINANT DNA RESEARCH AT THE PUBLIC HEARING IN THE DEPARTMENT OF HEALTH, EDUCATION AND WELFARE ON SEPTEMBER 15, 1978.

COMMENT

I represent Friends of the Earth in the litigation which is mentioned in the environmental impact assessment on the proposed revisions, and I am testifying here today on behalf of Friends of the Earth.

NEPA compliance

The major point I wish to make concerns compliance with the National Environmental Policy Act (NEPA). It is apparent from the testimony already given at this hearing that considerable controversy still surrounds the scientific aspects of recombinant DNA activities. NEPA is the best instrument available for the resolution of these controversies. It requires the preparation of an environmental impact statement for all major federal actions which could significantly affect the environment (including effects which are potentially beneficial as well as deleterious), and it requires that such a statement be prepared before taking action. The CEQ Guidelines and extensive HEW procedures in Chapter 30 of the General Administration Manual of HEW govern NEPA compliance. NEPA is a fundamental environmental law which provides the only mandatory formal mechanism for technology assessment. It also provides for public input in government decisions affecting the environment. The basic idea underlying NEPA is "think before you act", "tell everyone what you are thinking", and "act wisely".

From the beginning of the recombinant DNA program at the NIH, only the most feeble effort has been made to comply with NEPA. The final Environmental Impact Statement on the 1976 guidelines came out over a year after the guide-

lines were promulgated. The excuse that the guidelines were urgently needed does not exist with respect to the revisions and the efforts of the NIH thus far constitute a failure to comply with NEPA.

1. Necessity of preparing an Environmental Impact Statement

First, a thorough environmental impact statement on the proposed revisions is clearly required by the law. An environmental assessment is insufficient. The revisions are both major and significant, and the direction of change will significantly increase the possibility of affecting health and the environment. The comprehensive lowering of containment standards, the exemptions, the possibility of exceptions to prohibited experiments, all contribute to an increased risk to health and the environment. The revisions will lead to a significant expansion of recombinant research in addition to reduced safeguards on the several hundred recombinant DNA research projects already underway in this country. Moreover, the revisions will have worldwide impact on guidelines being used in Great Britain, the European continent, Japan, Israel, Australia, and likely even the USSR, because of the leading role the NIH has played in setting recombinant DNA research standards on a worldwide basis.

Even a casual perusal of the CEQ Guidelines and HEW procedures governing NEPA compliance demonstrates the necessity of a full environmental impact statement for the proposed revisions. Both the CEQ Guidelines, 40 CFR §1500.5 (a)(3), and the HEW General Administration Manual, Subsection 30-10-50 C.5., provide that modification or amendment of existing regulations, policies and programs are subject to NEPA requirements. In Dulles v. Volpe, 541 F.2d 442 (4th Cir. 1976), the court held that expanded airport use required an environmental impact statement and discussed the legislative history of NEPA:

> The House Committee was concerned that unless agencies were somehow forced to consider environmental factors in their decision making, "bureaucratic inertia" would frustrate the policies of the Act [footnote omitted]. These expressions of legislative purpose and concern indicate that Con-

> gress wanted the agencies to address environmental consequences not only in considering future projects but also in reviewing their present policies and programs, at least when expanding or revising them. [541 F. 2d at 446.]

The CEQ Guidelines provide that an environmental impact statement be prepared in all cases of proposed major actions, "the environmental impact of which is likely to be highly controversial". See, 40 CFR §1500.6(a). In Rucker v. Willis, 484 F.2d 158 (4th Cir. 1973), the court held that the term "controversial"

> should properly refer to cases where a substantial dispute exists as to the size, nature or effect of the major federal action rather than to the existence of opposition to a use. [484 F. 2d at 162.]

As made clear by the technical testimony at this hearing, the controversy over the proposed revisions goes to their nature and effect.

The CEQ Guidelines also provide for the preparation of an environmental impact statement when "it is reasonable to anticipate a cumulatively significant impact on the environment from Federal action". See, 40 CFR §1500.6(a). It is clear that the revisions will have cumulative impacts, expanding the scope of recombinant DNA research and facilitating the growing ability to manipulate the living environment. New biological products will be created and recombinant organisms will eventually be released into the environment. The research programs outlined by Robert Faust from the Department of Agriculture this morning indicate the kinds of developments which the revisions will allow and which must be studied and analyzed in an environmental impact statement. A thorough impact statement on the revisions is clearly required.

2. Inadequacy of the Environmental Impact Assessment

The second reason for concluding that there has not been NEPA compliance with respect to the proposed revised guidelines is that the Environmental Impact Assessment is wholly inadequate. This pro forma document is full of conclusory, biased, self-serving assertions and contains essentially no analysis.

The assessment has been constructed so as to give the appearance of a lengthy document, but it is disheartening to discover that it is mostly a reprint of the Director's Decision printed in the same issue of the Federal Register. Some portions of the Director's Decision are modified in the assessment with the result that the two documents are often contradictory. Illustrative is the discussion of the "somewhat arbitrary" character of the guidelines which is described in my second general recommendation.

A prime example of the lack of analysis concerns the basis for the exemptions stated on p. 33110:

> This [first exemption] is based on the safety of these experiments.... [T]he basis [for the second exemption] is occupational and environmental safety.... This [third exemption] was strongly endorsed by several public commentators on the basis of no hazard. The fourth exemption...allows certain of the experiments previously classified at P1+EK1 to be excluded, again with the strong endorsement of several public commentators on the basis of no hazard.

The emptiness of this "assessment" is obvious. Not much more is said in the relevant portions of the Director's Decision reprinted in the assessment on p. 33109. For the first exemption it is stated that:

> This is in recognition that "naked" DNA, which is rapidly inactivated in nature, is extremely unlikely to be hazardous under experimental conditions.

No data is given or studies cited which could substantiate this assertion, and as we have heard in testimony today, there is still scientific controversy over this hypothesis and there may be evidence to the contrary in the as yet unpublished data from the Martin-Rowe experiment performed at the NIH. Concerning the second exemption it is said that:

> This statement clarifies a category of "self-cloning" experiments that are considered safe enough to be excluded from the Guidelines.

Why they are considered safe enough, and what data supports this conclusion, is nowhere to be found. No further rationale is given for the other exemptions. None of these exemptions should be permitted until there is adequate risk as-

sessment and a detailed environmental impact statement prepared.

The discussion of E. coli K-12 illustrates the biased nature of the environmental impact assessment. From the testimony at today's hearing it is apparent that a number of issues concerning this organism have not been addressed. In addition, while the letter from Dr. Gorbach in regard to the Falmouth risk assessment workshop is quoted at length, no mention is made in the assessment of the letters from Drs. Levin, Goldstein and King which had differing views about the results of Falmouth. Dr. Bruce Levin, a population ecologist from the University of Massachusetts, who participated in the Falmouth workshop, stated that:

> I don't believe that evidence available through existing efforts at risk assessment is sufficient to justify a relaxation of the current NIH guidelines on recombinant DNA research or of the efforts to enforce them.

Dr. Richard Goldstein, Professor of Microbiology at Harvard Medical School, and Dr. Jonathan King, Professor of Microbiology at MIT, both attended the Falmouth workshop and jointly wrote to the Director of the NIH concerning that meeting:

> The meeting was serious and the participants did not belittle the problems associated with assessing risk in the construction of hybrid E. coli. The discussions were lively, with very frequent recognition that many classes of risk could neither be dismissed nor accurately assessed, without further experimentation.
>
> In terms of safety, we feel that there is no basis for a loosening of the NIH Guidelines until much more experimental data has been collected, and much broader experience and expertise brought to bear on the problems.

Both of these letters were published by the NIH in the Recombinant DNA Technical Bulletin, Vol. 1, No. 1, Fall 1977, but were utterly ignored in the environmental assessment. This kind of omission clearly violated the intent of NEPA.

While lengthy, though biased, attention is paid to E. coli K-12 in the assessment, there is virtually no analysis or assessment of the use of other hosts or vectors, some of which are already in use, such as, Bacillus subtilis, or have been developed for use, such as, Saccharomyces cerevisiae (baker's

yeast). Nevertheless, the environmental assessment leaves the impression that the question of safety has been resolved for the whole range of recombinant DNA work involving organisms besides E. coli, even though there has been nothing like the analysis of other organisms which has gone into E. coli K-12. This serious omission is illustrative of the self-serving nature of the environmental assessment.

Another glaring omission is the failure to discuss the striking differences in the guidelines of other countries, which was noted by Dr. W. J. Whelan in his testimony at this hearing. In addition, there is no detailed analysis of the numerous changes in containment levels, or explanations for specific changes and what, if any, data supports each change. Ten "criteria" are set out in the environmental assessment, but no attempt is made to explicate how they were applied in making changes in containment levels. This should be clearly and succinctly done for each change.

The preceding discussion is only illustrative of the kinds of defects in the environmental assessment. It is not meant to be exhaustive. As I have already stated, a detailed environmental impact statement must be prepared on the proposed revisions, and I recommend that the NIH consult with the many governmental agencies, private organizations and individuals who are concerned about recombinant DNA activities during the preparation of this document in order to insure that these concerns will be dealt with in a most efficient manner.

RECOMMENDATIONS

General recommendations

1. The "Recombinant DNA Research Guidelines" should be re-entitled, "Recombinant DNA Research Regulations". The guidelines have in fact been regulations all along, a point emphasized as long ago as 1976 by Peter Hutt. Calling

them what they are -- "regulations" -- would eliminate the ambiguity which leads many people to believe that they are only voluntary and would highlight the fact that only NIH funded research is regulated, a serious lacuna which must be remedied.

2. HEW should proceed with the promulgation of Parts I and IV and Section II.D. of the regulations, that is, the definitional, procedural and administrative sections -- with appropriate modifications. There is a need to improve the regulatory mechanism and create flexibility in the recombinant program. But it is premature to make any revisions in Part III and the remainder of Part II for two reasons. First, NEPA has not yet been complied with. Second, a convincing case has not yet been made for relaxation of containment standards. The meager efforts which have been made thus far to determine the risks involved in recombinant DNA activities have done little if anything to inspire public confidence. Even the one problem which has received a fair amount of attention, the use of E. coli K-12 as a host, still is a matter of scientific controversy, as is evident from the testimony received at this hearing. But E. coli K-12 is not the only host organism being used today and many others are contemplated for use in the near future, with no risk assessment having been conducted on these organisms.

With respect to containment levels, the Director's Decision, 43 Fed. Reg. 33058, states that, "In general, the classification may appear somewhat arbitrary...". In the Environmental Impact Assessment this statement has been changed to read, "In general, the classification <u>is</u> somewhat arbitrary" [43 Fed. Reg. 33117] (emphasis added). Immediately following, it is stated that:

> [The classification] depends in large part on the scientific judgment of the RAC rather than on demonstrable risk, because there is in fact no actual scientific evidence that there is a hazard in any recombinant DNA experiment. [43 Fed. Reg. 33117.]

This is not a valid rationale. "Judgment" which is scientific is based on sci-

entific evidence -- on experimental data, or on scientific theories themselves grounded in scientific evidence. If there is no experimental data, the "judgment" -- whatever else it may be -- is not scientific.

With respect to the 1976 guidelines, Dr. Maxine Singer of the National Cancer Institute stated in testimony on March 15, 1977, before the House Subcommittee on Health and the Environment that:

> Yes; the guidelines were put together, of course, in the absence of a lot of the information one needs.... I am just stating that it has been slow and a lot of the information needed for the guidelines was not available. Therefore, the committee which advised the Director of NIH for the guidelines had to make a certain number of judgments on insufficient facts and there are disagreements with the judgments that they made. If you take any particular recommendation in the guidelines, you will find knowledgeable scientists who feel that it is too stringent and you will find knowledgeable scientists who think that it is not stringent enough.

There has been very little new data developed since then and the rule of prudence and the need for a margin of safety -- basic principles of environmental and health regulation -- should rule out relaxation of the guidelines until sufficient data is developed and the outstanding scientific questions resolved. Again, with respect to the 1976 NIH guidelines and the British Guidelines, it was stated in the Report and Recommendations of the Second Meeting of the European Molecular Biology Organization Standing Advisory Committee on Recombinant DNA held in London on September 18-19, 1976, that:

> Both documents stress that, at present, there are no experimental data on which to base any objective estimates of the conjectured biohazards associated with recombinant DNA research. <u>Schemes for the classification of experiments according to their conjectured biohazard are, therefore, arbitrary</u>. Nevertheless both groups have proposed categories of containment for particular classes of experiments which are based upon the phylogenetic distance between the organisms involved. It is the opinion of this committee that the containment procedures envisaged in the two reports are sufficient to ensure that in vitro recombinant DNA research continues under conditions that provide adequate safeguards. [Emphasis added.]

The jump from the conclusion of arbitrariness, which is sound, to the conclusion of adequacy, is without logic. And the assumption concerning phylogenetic distance, upon which the NIH and British guidelines are based, itself has no

experimental foundation. The British Genetic Manipulation Advisory Group has declared about this assumption that:

> we have reservations about the implied proposition (which is, of course, central both to the UK and NIH guidelines) that hazards are necessarily less with nucleic acids from evolutionarily more distantly related sources. It has, for example, been argued that for many genes, such as those for histones or actin, there has been conservation over a wide evolutionary span, so that if such a gene were cloned any hazard its growth might pose would be the same whatever species was the source of the nucleic acid. [First Report of the Genetic Manipulation Advisory Group, p. 11 (May 1978).]

There is simply no reason to warrant a relaxation of the guidelines at the present time. A systematic program of risk assessment experimentation must be conducted upon which to base any loosening of containment standards. This is the only rational approach to establishing safeguards, and it is nothing more than what is mandated in the Charter of the Recombinant DNA Advisory Committee.

Specific recommendations

1. Risk assessment. There should be a requirement in the regulations for adequate risk assessment prior to any determinations on exemptions from the regulations, exceptions to prohibitions (unless the exception is itself for risk assessment research), and certification of all host-vector systems.

2. Higher containment. There should be provisions for higher containment, new prohibitions, and the revocation of exemptions and exceptions to prohibitions. As currently written, the proposed revisions have no procedures for acting should previously unperceived hazards arise or become apparent, except for the second paragraph of Part III and Section II-D-2-a, which provides for the rescinding of host-vector certification. Not only should there be a provision to cure this oversight, but it should provide for the prompt response to petitions. The following is a suggestion for such a provision:

> When information develops or circumstances indicate that permitted experiments have risks not previously recognized, such experiments may be prohibited or required to be performed at higher containment levels, notwithstanding any other provisions in these regulations. The Director may at

any time order a prohibition, higher containment, or the revocation of an exemption or exception to a prohibition upon a finding that there are potential risks which were not previously recognized. The Director may issue such an order with or without the recommendation of the RAC. Any person may petition the Director for a new prohibition, higher containment for an individual experiment or category of experiments, or the revocation of an exemption or exception to a prohibition. Within 15 days of receiving such petition the Director shall determine either that the request is or is not reasonable and issue an appropriate order, or refer the petition to the RAC for a recommendation at its next scheduled meeting.

The current language in the second paragraph of Part III permits the lowering of containment levels without requiring risk assessment, public participation and NEPA compliance. While these requirements should be mandatory for any relaxation of the guidelines, they should only be discretionary with respect to tightening of the guidelines. This is because new evidence of risks may necessitate urgent action in certain situations, but this would not be the case in lowering containment.

3. NEPA compliance. The regulations should specify NEPA compliance for all exceptions to prohibitions, exemptions, certification of all host-vector systems, and all situations in which containment requirements are to be set on a case by case basis, such as in Section III-B-1.

4. Exceptions to prohibitions. The provisions allowing exceptions should be split into two categories: one for risk assessment experiments, and one for other experiments. The documents accompanying the proposed revisions indicate that there is a need to permit exceptions for the purpose of risk assessment but fail to state or discuss the fact that as drafted, exceptions can be permitted for other purposes. The criteria for permitting an exception in the "other" category should be that there is "no significant risk and a clear social benefit to be realized". The language now in Section I-D-6 only says that weight shall be given to potential risks. This contrasts unfavorably with exemption I-E-4, which requires a finding of no significant risk, and is clearly inadequate. Of

course, a finding of no significant risk cannot be made with respect to the first category -- risk assessment experiments. But in both categories there should be a requirement of NEPA compliance.

5. Exemptions. As indicated in my comments on the environmental impact assessment, the making of specific exemptions in the guidelines is premature. However, there should be general language in the regulations providing for exemptions, after completion of risk assessment, NEPA compliance, public participation and a finding, based on experimental data, that the exemption presents no significant risk to health or the environment.

6. Certification of host-vector systems. In Section II-D2-b-(1), which specifies the data to be submitted for certification of HV-1 systems other than E. coli K-12, the following additional data should be required to be submitted: the organism's biological and ecological interactions with other organisms in its natural habitat; and its role, if any, in industrial, agricultural, and medical work, whether beneficial or harmful. This is vital information for assessing the risks of using an organism in recombinant DNA activities, in performing the kind of analysis required by NEPA, and in building a body of information for dealing with future problems.

7. Membership of the Recombinant DNA Advisory Committee. The composition of the RAC has already been discussed for Friends of the Earth by Pamela Lippe. I would only like to add that the Federal Advisory Committee Act, 5 U.S. C. App. I §5, requires that all federal advisory committees (1) be properly balanced in terms of the points of view represented and the functions to be served, and (2) not be inappropriately influenced by the appointing authority or by any special interest. Just in terms of point of view represented on the RAC, the critical scientific viewpoints

on the guidelines which were heard at today's hearing have never been represented on the RAC. They should receive adequate representation on the RAC, and by this is meant more than a token member.

33 Jackson Road
Somerville, Massachusetts
02145

September 21, 1978

Dr. Peter Libassi
General Counsel.
Department of Health, Education and Welfare
and
Chairperson of Recombinant DNA Review Committee

Dear Dr. Libassi:

The comments below are addressed to Secretary Califano's request for input regarding the Proposed Revised Recombinant DNA Research Guidelines published in the Federal Register, July 28, 1978. Because my technical background is limited, I will confine my comments to "the proposed revisions that establish the mechanisms for administering and revising the guidelines." My participation in the debates regarding recombinant DNA has included membership in the Coalition for Responsible Genetic Research; participation in the employee committee at the Harvard University Biological Laboratories which petitioned for worker representation on their IBC; and evaluation of the responses of Harvard University, Massachusetts Institute of Technology, and the City of Cambridge to the issue in terms of developing institutional mechanisms to enforce guidelines (while a student in the Health Policy and Management program at the Harvard School of Public Health).

Briefly, my comments are these:

1. The mandate of committees established to review hazards associated with recombinant DNA research, especially local institutional biosafety committees, should be extended to include all hazardous biological research. The same careful consideration of adequacy of facilities, researcher awareness and training, etc. accorded proposals for recombinant work should be required for work with viruses, cell cultures, and other biologically hazardous material, including appropriate MVA statements.

2. Local biosafety committees should have broader representation of non-professional research and technical staff, similar to the model developed by the Genetic Manipulation Advisory Group in Great Britain.

3. Institutional biosafety committees should have community representation. The recent, and tragic sequence of events surrounding the outbreak of small pox in Birmingham, England as a result of failure of laboratory containment practices, illustrates basis for continued community concern where hazardous research is being performed.

4. Employee and community representation must be selected by their own constituencies and appropriate training and education should be provided them through the institution so that their participation can be meaningful (see 6).

5. The employment of biosafety officers by institutions creates potential conflicts-of-interest in enforcing safety standards for workers in their institutions, and alternative arrangements must be sought. Biosafety officers should be responsible, not to their institutions or to NIH, but to OSHA, since their primary responsibility is monitoring the safety of the laboratory workplace for all researchers and support staff. The line of responsibility should be clear, and institutions conducting such research - public or private - should be willing to support safety personnel through salary but should not have hiring/firing control. In cases where research is sponsored by federal monies a proportion of overhead to the institution should be earmarked for support of safety personnel. When small, less endowed institutions are conducting research that is potentially hazardous, they should be allowed to form a consortium to jointly use services of a Biosafety Officer.

6. NIH and OSHA should jointly sponsor technical and educational assistance programs for biosafety committee-persons and officers. (A proportion of NIH budget appropriated for relevant research should be allocated for this purpose if no other funds are available).

continued

7. Facilities and training of laboratory workers in these facilities, should be certified through OSHA and NIH delegates prior to commencement of work involving potentially hazardous experiments.

8. A central registry of facilities and workers health records should be established, similar to that required by TOSCA Act.

9. Issues of application of RDNA experimentation for commercial use or other uses with societal impact should be dealt with by a separate process. Such decisions clearly involve ethical and political concerns and should not be made by a technical body nor by an agency responsible for promoting the research activity under consideration.

I hope these comments are clear. I am available to amplify or explain my positions should that be deemed appropriate by your committee. Thank-you for your consideration of these proposals.

Sincerely,

Clare D. Sullivan

cc: Kathy Mojerus
Dept. of Labor
OSHA
Directorate of Health Standards

Denis Chamot
Dept for Professional Employees
AFL-CIO

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

Program in Social Management of Technology

September 21, 1978

F. Peter Libassi, Esquire
General Counsel
Department of HEW
330 Independence Avenue S.W.
Washington, D.C. 20201

Dear Mr. Libassi:

I greatly appreciate the opportunity afforded me to testify before you and other members of the Department's Task Force on the Proposed Revisions of the Guidelines Governing Recombinant DNA Research. Subsequently, I realized that there is a portion of my submitted written testimony which may be somewhat confusing, and I am taking the opportunity of this letter to submit a clarification.

On page 19 of my written testimony I suggest language regarding the scope of concerns which ought to be within the purview of the IBCs. This should not be understood as conflicting with my earlier comments expressing reservation on the proposed scale of delegation of authority to the IBCs. I believe that federal approval (by an office such as ORNA) is necessary for all research proposals, experiments, changes in containment levels, and the like. The language I am suggesting on page 19 should be understood within the context of making it clear that the IBCs can supplement the NIH guidelines by local institutional policies. Thus the central phrase in the language I suggest is "compliance with NIH guidelines," and thus all the issues as to what the guidelines will contain, etc., are, in effect, incorporated by reference.

If I can be of any further assistance to the Departmental review group and your staff, in working on these issues, please contact me.

Very truly yours,

Philip L. Bereano

Philip L. Bereano
Associate Professor

PLB:rl

[A-247]

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80 East Concord Street
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Department of Socio-Medical Sciences
and Community Medicine

September 22, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD. 20014

Dear Dr. Fredrickson:

In response to your call for public comment on the Proposed revisions of the NIH guidelines for Recombinant DNA research, published in the Federal Register on July 28, 1978, I would like to offer the following observations. I have confined myself to the areas where I have most expertise, but I note here that there are other important issues, such as the generic designations in the exempt list of "exchangers", which are glaring defects given our present state of knowledge.

It is my conviction that the proposed revisions, like their predecessors, will contribute nothing to another of the gaps in our current knowledge, and this prompts these comments. I am speaking of the possible risks to human health and well-being that are posed by Recombinant DNA research, and their detection if they should be realized. My comments cover two areas: (1) The assurance of safe procedures in Recombinant DNA laboratory work; (2) the detection of untoward events should these procedures fail.

(1) The assurance of safe procedures. This has been an area of concern in the past, and has resulted in additional detail on facility certification, periodic inspections and monitoring being made available in the supplementary "Laboratory Safety Monograph." The question of uniform training and certification for R-DNA workers appears to be still open, however. The fact that many of these workers are molecular biologists, unused to and untrained in standard aseptic technique adds special urgency to this problem. Even when such training is part of the background of a laboratory worker, constant surveillance and specific requirements to cover individual kinds of laboratory prodecures are necessary. Indeed, even such high-containment facilities as Fort Detrick have suffered hundreds of laboratory-acquired infections with very pathogenic organisms. One of the first fruits of the concern over R-DNA research was the 1973 Biohazards Conference at Cold Spring Harbor. It was emphasized by CDC personnel at that very early date that their experience clearly indicated that the "education of laboratory workers in techniques and introduction of equipment with special safety features" was especially important in keeping laboratory acquired infections to a "minimum." I note in passing that that "minimum" is not by any means negligible. The use of a specially trained biohazards officer and the introduction of special laboratory safety guidelines in combination with high-containment facilities succeeded in reducing the incidence of laboratory-acquired infections by three-fourths, but that incidence still stands at 1 case/250 workers/year. When one considers the likely number of R-DNA workers and the much less

rigorous level of their training, it is obvious that spread of R-DNA-molecule-containing organisms outside the laboratory is almost inevitable, if the host organism can find a suitable ecological niche. We know incredibly little about the ecology of organisms like E. coli and the few experiments with healthy volunteers are entirely insufficient to make any important policy decisions.

It is stated in the Federal Register notice (p. 33128, col 3) that training courses for biosafety officers and standards of training and uniform certification procedures are now being undertaken "carefully and in stages." While this deliberation and care are most appropriate, until this process is completed there should be no relaxation of any kind of the NIH guidelines, while at the same time those requirements in the Proposed Revisions that strengthen safety requirements, like the prohibition of mouth-pipetting should be retained.

Recommendation: There should be no change in the current NIH guidelines unless and until uniform and consistent training guidelines and certification procedures are established for biosafety officers and all R-DNA laboratory workers at the P-2 and higher level.

(2) The detection of untoward events (epidemiological monitoring):

The recent tragic case in England of small-pox acquired by a non-laboratory worker on the next floor from the laboratory where the virus was under investigation demonstrates once again that there is much to be learned about how organisms might escape from supposedly secure facilities (to date the mechanism of the small-pox episode has not been determined). This underlines the urgency and

necessity of establishing uniform and consistent surveillance of R-DNA workers and their contacts for untoward effects associated with R-DNA laboratory activities. Again, the full detailing of (required?) monitoring procedures will apparently be left until later. For the same reasons as given under point (1) above, no relaxation of the guidelines should take place until this monitoring is instituted. Preferably, all work should stop until this frequently called for and necessary activity is begun, but I realize this is not feasible given the current situation. This shows once again how necessary it is to do these things right from the outset.

Moreover, the lack of monitoring and surveillance almost guarantees that R-DNA research will appear safe, whether or not it is. This is because there will be virtually no way to detect an adverse event if it occurs. An historical example is available in the SV-40 contaminated adenovirus and polio vaccines that could, even now, be causing catastrophic illness beyond our ability to detect it because no means of follow-up of the exposed individuals was instituted.

Recommendation: No relaxation or "increased flexibility" in the NIH guidelines be permitted until an adequate, consistent and uniform epidemiological monitoring and surveillance program is instituted and administered at the national level, and which includes, at the least, the following elements:

(i) A definition of the monitored cohort which will include not only all R-DNA workers but also all ancillary workers, such as maintenance, glassware washers, etc. Immediate household members of these should also be included. There should be a mandatory

central register administered by CDC that includes approximate level of exposure or proximity to hazard, as well as the usual demographic information.

(ii) A means of long-term follow-up should be established.

(iii) Suitable outcome events should be established and monitored at periodic intervals. Special sample surveys should also be possible as knowledge increases.

I appreciate the opportunity to comment on the proposed guidelines.

Sincerely yours,

David Ozonoff, MD

David Ozonoff, MD, MPH
Public Health Program

pad

CALIFORNIA INSTITUTE OF TECHNOLOGY

PASADENA, CALIFORNIA 91125

DIVISION OF BIOLOGY 156-29

September 22, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Sir:

At its last meeting, our Institute Biohazards Committee discussed the Proposed Revised Guidelines published in the Federal Register on Friday, July 29, 1978. Comments about these Guidelines were favorable with one exception. It is unclear to our Committee why Section IV-A-1-e (concerning medical surveillance) is so written. On the one hand, at the Falmouth Conference, the conferees agreed unanimously that E. coli K12 cannot be converted into an epidemic pathogen by laboratory manipulations with DNA inserts. On the other hand, any risk associated with recombinant DNA work is purely hypothetical and no medical procedures exist to test for such risks. Thus, taking of routine serum samples, collection of detailed medical records, and involvement of the local public health authorities would seem to serve no useful function while being expensive, both in terms of time and money. Although it is true that the Guidelines do not require such detailed surveillance, but merely suggest it, it is also true that such a suggestion as part of the Guidelines carries the implication that such surveillance should be maintained. The experience of the past several years has been that recombinant DNA work is safe, and to introduce at this time more detailed requirements for such work seems unjustified. It would seem sufficient to maintain the current level of medical surveillance, namely, that any serious or extended illness be investigated. We are also of the opinion that some of the medical surveillance procedures detailed on page 203 of the accompanying monograph on laboratory safety constitutes a serious invasion of privacy which is unjustified in the absence of compelling reasons to collect such data.

Sincerely,

James H. Strauss

James H. Strauss
Associate Professor
Chairman, Institute Biohazards Committee

JHS gc

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

STANFORD UNIVERSITY SCHOOL OF MEDICINE
Department of Medicine

September 22, 1978

Dr. Donald Frederickson
Director
National Institutes of Health
Bethesda, MD 20014

Dear Don:

I am writing to comment on the proposed new guidelines governing research with recombinant organisms. I appreciate the efforts which have been made to define and limit potential harms, and I am encouraged by the absence of harms in the experiments conducted thus far. I also appreciate the efforts which have been made to establish reasonable guidelines so that important research can continue without unreasonable restrictions. Nonetheless, I think there are substantial problems which are inadequately addressed by the proposed new guidelines. The following comments specifically do not address proposed modification of containment requirements for particular types of experiments; I am skeptical about some of the reasons for those changes but do not consider myself qualified to criticize them reliably. My concerns are:

1. Epidemiology. To date we have encouraging evidence that the techniques have not produced pathogenic organisms. However, the evidence is quite incomplete. First, the rDNA experiments which have been done to date have been mainly of the potentially safest types; those requiring more effective containment have by and large not been performed. Second, the published epidemiological analyses of exposed persons involve only a few of the active laboratories and cover brief time periods of exposure. We have essentially no information about the effect of chronic, low dose exposure to recombinant organisms. Third, virtually all experiments to date have been small in scale; it is entirely possible that large scale experiments such as will occur in industry will create different epidemiological problems and perhaps greater risks. Fourth, the proposed guidelines require no formal epidemiological study and appear to leave health monitoring practices entirely undefined and voluntary at involved institutions. Therefore it seems to me that the guidelines' approach to the monitoring and study of the potential spread and effects of recombinant organisms is seriously inadequate. On both scientific and public policy grounds, this is a genuine deficiency.

2. Public participation in decision making. I understand that recombinant experimentation is only one way in which potentially dangerous organisms can be created through laboratory experimentation or commercial

development. Nonetheless, this type of experimentation has raised issues of safety for biological experimentation in general, and is therefore an appropriate place to begin devising desirable regulatory policies. The issue is all the more focused because of the implications of genetic engineering in higher animals possessed by the recombinant technology.

In my view, the integrity of science requires that decisions which could have great effect upon the public well-being should be made with sound public understanding and assent. The new guidelines do not assure significant public participation at either federal or local levels. I think that the federal government should set the example by establishing a representative public body to advice on this and related policy issues concerning new biological techniques, and I also think that the guidelines should require significant public participation in Institutional Biohazard Committees. Only in these ways can useful public contributions be obtained and a level of trust established between the scientific community and the citizens.

3. Commercial applications. Whatever problems exist with recombinant technology, they are likely to be intensified during large scale commercial exploitation. The present guidelines speak only of voluntary industrial observation of regulations. I consider this grossly inadequate and would suggest that HEW either act administratively to assure industrial compliance or introduce legislation requiring it.

There is no way to avoid uncertainty on virtually all issues of safety of recombinant work or of soundness in application of the techniques to commercial or medical purposes. Each new experiment or large scale process will potentially create new problems. If anything is certain, it is that uncertainty will remain with us. Prudence therefore requires careful epidemiological study of our experience in both small and large scale operations, citizens' understanding of and concurrence with the purposes of the work and the risks which should be run, and uniform compliance with reasonable regulations by all agencies employing recombinant techniques. In each of these areas, the new guidelines are deficient, often seriously so.

I would urge that the guidelines be amended to: (1) mandate effective health monitoring practices at each involved institution, (2) mandate carefully designed epidemiological studies for various classes of recombinant experiments to be done under HEW auspices, (3) establish a federal advisory committee with broad public representation, (4) increase and mandate public participation in Institutional Biohazard Committees and (5) require industrial compliance with the guidelines. Some of these proposals can be accomplished easily; others will require considerable thought. Many of us will be willing to contribute to that thought should you wish us to do so.

Thank you for considering these suggestions.

Warmest regards.

Sincerely,

Hal

Halsted R. Holman, M.D.
Professor of Medicine
HRH:bso
cc: Senator Edward M. Kennedy Senator Adlai Stevenson
Mr. Peter Libassi
Dr. Julius Richmond

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN 49001, U S A

GENERAL LAW

Office of
MURRAY D. WELCH, JR.
Associate General Counsel
and Director

TELEPHONE (616) 323-6068

September 22, 1978

Dr. Donald Fredrickson
Director, National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

"Proposed Revised Guidelines" for recombinant DNA research were published in the Federal Register for July 28, 1978.[1] The Upjohn Company supports these Guidelines. While we believe that they are both reasonable and appropriate, we have a few suggestions which, in our opinion, would improve the Guidelines. They are:

1. I-E-3. Amend this section to read:

   I-E-3. Those that consist entirely of DNA from a prokaryotic host, including its indigenous plasmids or viruses, when propagated only in that host [(or closely related strain of the same species)] or another organism in the same genus; also those that consist entirely of DNA from a eukaryotic host, including its chloroplasts, mitochondria, or plasmids (but excluding viruses), when propagated only in that host (or a closely related strain of the same species).

   Note: Omitted language is in [brackets]; new language is underlined. Hereafter, this format will be used.

   Justification

   Under the Proposed Revised Guidelines, many experiments involving the insertion of recombinant DNA derived from a non-pathogenic prokaryote into another closely related non-pathogenic prokaryote will not be permitted even under P-4 physical containment. Prohibition of these types of experiments will severely limit the

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[1] The Guidelines would apply if the institution receives NIH funds for recombinant DNA research projects (The Upjohn Company receives no such funds). Ref. IV-C-1, pg. 33087; or, if the institution voluntarily registers with NIH, Ref. IV-C-2, pg. 33087.

ability of pharmaceutical firms to design new and more effective antibiotics using recombinant DNA technology. For example, important new antibiotics could be developed by inserting, into known antibiotic producing organisms, genes coding for enzymes to modify the original antibiotics. In order to develop new antibiotics utilizing this technology, however, many different antibiotic producers will have to be screened, most of which are members of the genus Streptomyces. The fact that it is clearly not feasible to develop separate HV-1 systems for all of these organisms coupled with the realization that no biohazard would be generated by these experiments, indicates that the framers of the revised Guidelines have not adequately considered the potential benefits and risks from these types of experiments. The proposed amendment would allow much of this work to proceed without increasing the hypothetical risk to workers, the public, or the environment.

2. IV-A-2-f. Amend this section to read:

IV-A-2-f. Keep minutes of meetings and, upon request, make them available to the public (except confidential or proprietary data and information).

Justification

The Upjohn Company has voluntarily established an Institutional Biosafety Committee (IBC) with twelve members, four of whom are from the local community and are not employed by the company. In Section IV-A-2 of the Proposed Revised Guidelines, it is stated that "The principal functions of the IBC are to review and oversee all recombinant DNA projects and to advise the institution and ORDA whether the proposals and the research comply with the NIH Guidelines." Experience has shown that in order for this committee to perform these functions, it will be necessary for it to consider confidential or proprietary data and information belonging to the company which are valuable company assets. At the time of consideration, these assets may not be protected by patents. The company and the IBC believe that the minutes of the committee should contain at least the substance of the data and information it considered in performing these functions. However, if the minutes are made available to the public, these assets could be damaged, i.e., the data and information in the minutes would be available to competitors and premature disclosure might prevent the company from obtaining adequate protection for its inventions under the patent laws of the

United States and many foreign countries, particularly when the information at the time the minutes are available to the public is not adequate to support a patent application. Such premature disclosure would be particularly harmful if one desired to obtain patent protection in most significant foreign countries. Furthermore, not all confidential or proprietary data and information are patentable. In the latter case, such data and information are regarded as trade secrets and even though unpatented, they remain very valuable assets. The company does not object to the principle of providing some means for the public and the local community to be informed regarding its DNA research; however, it believes that there is more than one way to accomplish this objective. Thus, the public may be informed directly or through representatives. The company has no objection to informing the public directly by making the minutes available for their inspection provided this does not damage valuable company assets. However, if this would damage company assets, we believe that the interests of the public and the local community are adequately protected through the public representatives on the IBC. We believe that the public and the company can rely on the good judgment of the public representatives on the IBC to determine whether or not it is necessary to make public any confidential or proprietary data and information. The proposed amendment would allow the use of the second method for informing the public while preserving the company's assets, so long as that was not inconsistent with the public interest. It is noted that the company has more public representatives on its IBC than is required by the Proposed Revised Guidelines, i.e., the Guidelines would require only one public representative. Ref. IV-A-2, pg. 33085.

3. IV-C-3-a-(4). Amend this section to read:

IV-C-3-a-(4). Necessary, in the judgment of the Secretary or his designee, [the] to protect the public or the environment against an unreasonable risk of injury to health or the environment. The Secretary or his designee shall consult with the person who has submitted the information or who would be affected by disclosure before determining whether or not such information will be released under this subsection. If the Secretary or his designee rejects the person's request that such information not be released, the decision constitutes final agency action that is subject to judicial review pursuant to 5 U.S.C. chapter 7. The person affected will be permitted 5 days after receipt of notification of such

decision within which to institute suit in a United States District Court to enjoin release of the records involved. If suit is brought, the Secretary or his designee will not disclose the records involved until the matter and all related appeals have been concluded.

Justification

Persons who are engaged in recombinant DNA research and to whom the Proposed Revised Guidelines would apply only if they voluntarily registered under IV-C-2, would be more likely to register if they could be assured that their confidential or proprietary data and information would not be disclosed unnecessarily. Furthermore, the suggestion in IV-C-4 that the institution "consider applying for a patent before submitting information to DHEW" is not practical because the institution, if it voluntarily registered its DNA research projects with NIH, in many cases would be required to submit confidential or proprietary data and information to ORDA before beginning such experiments and in all other cases ORDA will receive the information as soon as approval is granted by the IBC. Experience has shown that in many cases, the information that is available prior to beginning an experiment is often inadequate to support a patent application. Thus, DHEW could disclose the confidential or proprietary data and information before an institution could obtain adequate protection under the patent laws of the United States or many foreign countries. This is especially true with respect to the patent laws of certain foreign countries. As previously noted, not all confidential or proprietary data and information are patentable. In the latter case, such data and information are regarded as trade secrets and even though unpatented they can be very valuable assets. The proposed amendment is based on the Public Information Regulations of the Federal Food and Drug Administration (21 C.F.R. 20.45; 20.46). If adopted, it is submitted that it would encourage institutions to voluntarily register NDA research projects with NIH.

Finally, we wish to note that we are in complete agreement with the principle of flexibility that has been built into the Proposed Revised Guidelines. We believe that the Director of the National Institutes of Health should have the authority given to him in Section I-E-5, for example, to exempt "other classes of recombinant DNA molecules if the Director, NIH, on the recommendation of the

Recombinant DNA Advisory Committee, after appropriate notice and opportunity for public comment, finds that they do not present a significant risk to health or the environment." The Guidelines, in our opinion, should not be rigid or require the Director of NIH to resort to time-consuming and bureaucratic procedures in order to change them when changes are necessary to reflect increased knowledge and experience with recombinant DNA research.

Sincerely,

Murray D. Welch, Jr.

Murray D. Welch, Jr.

pr

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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SCHOOL OF MEDICINE SAN FRANCISCO, CALIFORNIA 94143

September 22, 1978

Director, National Institutes of Health
Building 1, Room 124
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Director:

I am writing to object to the lowering of the containment level for animal virus DNA experiments as described on page 33077 of the proposed revised guidelines for recombinant DNA research on general microbiological grounds coupled with concern regarding certain specific provisions.

On general grounds, it was stated that the rationale for lowering the containment is "cloning the whole or any part of a virus must logically be less dangerous than working with the whole virus itself, which is done routinely". (Science 201:600, 1978). I think that working with the whole virus can be significantly less dangerous than cloning the whole virus genome for three reasons: 1) whole virus can elicit the production of protective antibodies and 2) whole virus with its protein coat is subject to the "biological barrier" which can limit infection across species lines, and 3) whole virus is frequently eliminated from the body after infection. It can be argued, therefore, that the presence of animal virus DNA within *E. coli*, which may establish itself in the intestinal tract, subverts these normal protective devices and may be more dangerous than working with the virus itself.

My concerns regarding specific provisions are:

1) Page 33077, Section III-A-2-a-(1)-(a)-(2)-(a) Hepatitis B

   Since it is possible that the subgenomic fragment could contain the DNA which codes for the protein which causes disease, it seems advisable to be more cautious than P1 + EKI with this pathogen.

   In addition, no mention is made of hepatitis A virus in any section.

2) Page 33077, Section III-A-2-a-(1)-(b)-(1)-a

   1) I think our ability to accurately ensure that a piece of DNA is non-transforming is not good enough to allow P1 + EKI for these potential human transforming viruses.
   2) I think the requirements in the next section regarding the entire transforming gene and the entire virus are not stringent enough. An EK-2 host should be used.
   3) No provision is made for Herpes simplex types 1 and 2 which can transform cells in culture.

3) Page 33077, Section III-A-2-a-(1)-(B)-(2)-b

An EK-2 host should be used with recombinants of the whole viral genome.

4) Page 33078, Section III-A-2-a-(2)-a-(1)-(a)
   1) I have the same thoughts in this section as those expressed in item 2 regarding our ability to determine "non-transformation".
   2) In the (b) section -- an EK-2 host should be used with the entire transforming gene.
   3) In the (c) section -- the EK-1 host alternative should be deleted.

5) Page 33078, Section III-A-2-a-(2)-(a)-(2)-(b)

An EK-2 host should be used with entire transforming gene and with whole virus genome.

6) Page 33078, Section III-A-2-a-(2)-(b)- Negative Strand RNA viruses

No special provision is made for rabies virus.

In addition, no special provision is made for human encephalitis viruses, some of which are RNA(+) strand and others of which are (maybe) RNA(-) strand.

In closing, I should add that I have read the report of the U.S.-E.M.B.O. workshop on pages 33159-33169 but think that our knowledge of these structural and replicative aspects are too primitive to be as certain as the authors indicate.

This opinion is mine and not necessarily that of other members of the campus biosafety committee of which I am a member.

Sincerely yours,

Warren Levinson

Warren Levinson, M.D., Ph.D.
Professor of Microbiology and Immunology

WL:jh
cc: Dr. J. Cleaver
Chair
UCSF Biosafety Committee

September 22, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, MD

Dear Dr. Fredrickson:

I am writing to indicate my overall support for the PRG-NIH as published in the *Federal Register*, Volume 43, Number 146, July 28, 1978. As a scientist involved in recombinant DNA research, I have continually supported the concept of NIH promulgated guidelines. The proposed NIH revisions to the current guidelines are generally very well reasoned and clearly reflect the substantial body of new knowledge acquired over the last several years, as well as the recognition by those formulating policy of a large body of information relating to epidemiology and infectious disease.

While generally in support of the PRG-NIH, I do wish to offer several comments which I feel merit consideration.

1. Section I-E-3 (page 33070, column II, paragraph 5) exempts from the PRG-NIH recombinant DNA molecules consisting entirely of DNA from a prokaryotic host, including indigenous (emphasis added) plasmids or viruses when propagated in that host (or closely related strain of the same species). Your Decision of the Director, dated July 19, 1975, page 33050, paragraph 4, indicates indigenous to mean "found in Nature." I would like to suggest that, if a plasmid from one strain or species can be transferred to another strain or species in the laboratory, then recombinant DNA experiments involving that second host and plasmid should also be exempt from the guidelines. Footnote 35, page 33088, to section III-B-2, page 33080, indicates that plasmid transfer may be less stringent a definition than applied to section I-E-4. However, since I-E-4 pertains to interspecies recombination, and I-E-3 applies to "self-cloning," it seems reasonable that "self-cloning" with plasmids transferred in the laboratory by natural genetic processes such as conjugation are clearly consistent with the intent of the PRG-NIH and pose no conceivable risk to the investigator or the environment.

2. On page 33096, as part of the Summary of the NIH-EIA... under "Environmental Impact of Proposed Action," you use the term "conjectural hazards." To the extent possible, I feel the terms "conjectural" or "speculative," rather than "potential," are preferred adjectives to

Cetus Corporation, 600 Bancroft Way, Berkeley, California 94710 Phone: (415) 549-3300

the terms "hazards" or "risks," and should appear uniformly throughout the PRG-NIH. While this may only be semantic, I believe that it more precisely reflects our current knowledge and understanding.

3. I specifically want to express my strong approval for the change that will enable non-NIH funded institutions (section IV-C-2 and Appendix C, IV-C) to seek the advice and council of RAC, ORDA and the Office of Research Safety, NCI (section IV-C-2). This section will aid our ability to comply with the specifics as well as the intent of the PRG-NIH.

4. One portion of section IV-A-2, which deals with the membership of institutional biosafety committees, may pose a particular problem for private industry. PRG-NIH precludes any member of an IBC from participating in the review or approval of a project in which he/she has direct financial interest. In an effort to prevent possible conflicts of interest (clearly, a desirable goal), PRG-NIH could be interpreted as requiring all decisions to be made by "noninstitutional" IBC members. Since all management, directors, scientists and staff of a private corporation could or would have direct financial interest in any scientific project carried out by their firm, I suggest that the term "direct financial interest" be eliminated at least as far as private industry is concerned.

5. There is an aspect of PRG-NIH which I find a disturbing departure from both the 1976 guidelines and PRG-RAC. While I thoroughly support the effort to involve the public and to seek wide input for discussions of policy, I can find little reason to require public comment and response for purely scientific evaluations (e.g., I-E-4, IV-B-1-c, IV-B-1-d). Furthermore, while more decentralization in certain areas appears in PRG-NIH (e.g., IV-A-2-a, IV-A-2-b), in other areas there appears to be a substantial shift in decision-making power to ORDA and the Director exclusively that seem both unnecessary and unwise. Your Decision Document specifically states, "Flexibility, however, remains essential to avoid unnecessary and protracted delays in decision making." For example, it seems very likely that a very large number of new HV1 vectors will be proposed for many recombinant DNA experiments. A more flexible approach (than requiring approval, publication for comment, public hearings, and finally certification for HV1!) would permit RAC to approve and certify new HV1 host vector systems based on the requirements in PRG-NIH after review of the submitted scientific evidence.

   Similarly, I believe that unwarranted delays could be avoided if program directors for NSF, DOE, USDA, etc. sponsored recombinant DNA research projects similarly were able to authorize use of alternate HV1 systems after seeking the advice of RAC or some other scientific

advisory body. In addition, other program directors (USDA, NSF, etc.) should be able to authorize exemptions (specifically, under I-E-4) based on review by RAC or another scientifically competent review panel. Finally, I feel that greater latitude should be given to IBCs for assignment of levels of containment to experiments not explicitly covered by the guidelines. Under PRG-NIH, such experiments must be submitted in an MUA to ORDA, reviewed by RAC (Appendix C, section E-2) and then approved by the Director of NIH (IV-B-1-e).

While all possible experiments could never be foreseen, PRG-NIH is considerably improved over the current guidelines in providing greater detail in the classification of experiments. More importantly, however, the background information and discussion in the footnotes and accompanying the PRG-NIH in the form of the Decision Document and supporting appendices serve to provide a well-reasoned conceptual framework for the assignment of containment levels to experiments not specifically dealt with in the guidelines. Thus, the guidelines wind up being just that - guidelines. On the other hand, it seems that PRG-NIH says, "nothing expressly permitted is strictly forbidden...until approved," rather than reasonable persons (IBCs) following the framework provided by PRG-NIH can determine appropriate containment levels for experiments not expressly covered by the guidelines. These decisions, of course, would be subject to review by ORDA and, if necessary, RAC.

6. There is an additional complication arising from the increased centralization of decision-making authority and the prohibition of everything not expressly permitted in the PRG-NIH. There is an apparent paradox that obviously nonhazardous experiments which are currently permitted will have to stop, pending what will undoubtedly be a long, tedious procedure for subsequent approval. For example, cloning of DNA segments from one *Streptomyces* species into another *Streptomyces* species has been approved by both IBCs and NSF as clearly falling within the intent of the current guidelines. In the PRG-NIH, exemption I-E-4 might be cited to permit such manipulations. Unfortunately, Appendix A fails to list <u>any</u> *Streptomyces* species. Further, the prohibition on the use of conjugative HV1 vectors will substantially retard the development of plasmids such as SCP2 for cloning vectors.

The simplest solution to this problem is the institution of HV0 as a level of biological containment. HV0's could be approved by IBCs for use as alternate host-vector systems as long as the host were nonpathogenic. Vectors would not necessarily have to provide the level of containment required for HV1 (e.g., nontransmissibility of plasmids). Finally, analogous to the suggestion in Appendix G (II-D-a), all experiments conducted with HV0 systems require a one-step higher level of physical containment than the comparable experiment performed with an HV1 system.

I want to thank you very much for keeping us informed during the last twelve months of the progress in revisions in the NIH guidelines. Unfortunately, prior commitments prevent my attendance at the September 15 meeting.

Sincerely yours,

David H. Gelfand, Ph.D.
Director, Recombinant Molecular
Research

DHG/eaj

UNIVERSITY OF SOUTH CAROLINA

COLUMBIA, S. C. 29208

DEPARTMENT OF BIOLOGY

September 22, 1978

Dr. Donald S. Fredrickson
Director
NIH

Dear Dr. Fredrickson:

I wrote you on August 21 about the Recombinant DNA guidelines and enclosed a manuscript about gene transfer in Caulobacter crescentus. I have just received a letter from Irving Crawford, one of the editors of the journal Genetics informing me that the manuscript has been found suitable for publication. Therefore, the manuscript I sent you can be considered "in press".

I would appreciate your doing all you can to ensure that C. Crescentus is included in the list of exempt organisms in section I-E-4 of Appendix A of the revised Guidelines when they go into effect.

Sincerely,

Bert Ely

Bert Ely
Assistant Professor

BE/mpw

[A-267]

The University of South Carolina: USC Aiken; USC Salkehatchie, Allendale; USC Beaufort; USC Columbia; Coastal Carolina College, Conway; USC Lancaster; USC Spartanburg; USC Sumter; USC Union; and the Military Campus.

September 22, 1978

Joel A. Ventresca
202 Grattan Street
San Francisco, California 94117
(415) 731-1434

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I have the following questions on the new proposed revised guidelines for recombinant DNA research:

Question 1:

"There is no known instance in which a hazardous agent has been created by recombinant DNA technology." (page 33102)

What is the probability that if a hazardous agent has been created by recombinant DNA technology that we would know about it? Probability is based upon understanding variables. How many variables are at play in the recombinant DNA process? Specifically, what are the variables? Can they be listed? Do we fully comprehend all the variables involved in the recombinant DNA process?

Question 2:

"There are <u>various indications</u> that both host bacteria and plasmid or virus vectors containing inserted foreign DNA are less likely to survive and multiply than are the original organisms, except for the very unusual instances where the foreign DNA supplies some function, such as antibiotic resistance, that favors the organism in a particular, non-natural environment." (page 33102)

What are the "various indications" that both host bacteria and plasmid or virus vectors containing inserted foreign DNA are less likely to survive and multiply than are the origninal organisms? What is the probability that the foreign DNA supplies some function that favors the organism? Do we know the probability of this?

Question 3:

"There is a chance that a bacterial host of recombinant DNA will grow more rapidly than if it were lacking the foreign DNA...(The calculation given above can be applied here also.)" (page 33102)

Would the calculation then read as follows?

Assume that a natural organism constitutes 90% of a population, but grows 10% less rapidly than a new organism counterpart. The natural organism will drop from a concentration of 90% to a concentration of 0.0001% (1 part in 1,000,000) in 207 generations. If the generation time of the new organism is 1 hour, this amounts to about $8\frac{1}{2}$ days.

And if not, how would the calculation written on page 33102 be applied to the statement written above in quotes?

Question 4:

"Inadvertent dispersal of such viruses outside the laboratory might result in entry of the recombinant DNA into cells of living organisms." (page 33103)

If dispersal of recombinant DNA outside the laboratory has happened and/or will happen what is the probability that we would know about it? How would we know? How would we not know?

Question 5:

Are the proposed Federal guidelines substantially less restrictive than the current ones? If so, can the parts of the current Federal guidelines that are being proposed as being less restrictive be listed and the specific reasons why included next to them?

Question 6:

What specific types of experiments in recombinant DNA research are prohibited by the proposed revised Federal guidelines? In each type of banned experiment why is the experiment prohibited (specifically what are the reasons)?

Question 7:

"Only limited information concerning the effect of foreign DNA insertions on the survival or transferability of plasmid and viral vectors is available." (page 33103)
"...very little is understood about the totality of the genetic makeup of a given organism or species contributes to its competitive advantage ..." (page 33102)
"...plasmids, the factors contributing to their maintenance or loss from cells in natural environments, even without insertion of a foreign DNA, are not clearly understood." (page 33102)
"Experiments carried out during the last few years have yielded only minimal information on the stability of plasmids containing foreign DNA in host cells, or on the stability of the foreign fragment itself." (page 33102)
"...consideration of the loss of the plasmids in natural environments- the important point for matters of safety- the stability of the plasmid or recombined DNA under ordinary, or nonselective, conditions needs to be known." (page 33102)
"...no generalization concerning the effect of a foreign DNA fragment on transferability can be made." (page 33103)

With these statements in mind, I would like to see a more complete description of what we do not know about recombinant DNA research. What are the areas of our ignorance? What do we clearly, positively, and undisputedly know? What areas in recombinant DNA technology are disputed? What is unknown? What are the barriers or boundaries of our ignorance?

Question 8:

An experiment at the University of California San Francisco Medical Center was destroyed by high-temperature sterilization in March 1977 because the test was in violation of standards set up by the Federal government to insure the public's safety from recombinant DNA research.

In the September 1978 issue of The Sciences published by the New York Academy of Sciences an article by Boyce Rensberger entitled "What Makes Science News?" page ten states, "At The Times, we once ran a story about Creutzfeldt-Jakob disease, a rare degenerative disease of the central nervous system that is believed to be caused by a virus. It had been found that surgical instruments that touched the brains of victims could pick up the virus, which was not killed by conventional sterilization methods, and transmit it to the brians of others, who then came down with the invariably fatal disease."

Is it possible that recombinant DNA technology could create an agent or carrier that was not killed by conventional sterilization methods?

Question 9:

The two major recombinant DNA researchers at the University of California San Francisco Medical Center did not tell the truth at a press confrerence on May 23, 1977 that their research was carried out within the safety procedures established by the National Institutes of Health. In fact, the researchers Dr. Howard M. Goodman, Professor of Biochemistry, and Dr. William J. Rutter, Chairman of the Department of Biochemistry and Biophysics, had violated the safety procedures just three months before (documented in Science September 30, 1977).

This clear deception on the part of these researchers is documented in the following newspaper articles: San Francisco Chronicle May 24 and September 27, 1977 by Science Correspondent David Perlman, and San Francisco Examiner May 24 and September 27, 1977 by Science Writer Walter Barney.

How will the proposed new guidelines deal with a situation like this? What if any sanctions will be taken against researchers who knowingly mislead and/or deceive the public?

Question 10:

I am enclosing a leaflet I wrote in October 1977 on the subject of recombinant DNA research at the University of California San Francisco Medical Center. Albert R. Jonsen, Vice-Chairman (November 1976) of the institutional Biosafety Committee on the San Francisco campus of the University of California, called this leaflet "a tissue of falsehoods." The information on the leaflet was primarily obtained from the New York Times, Science and Smithsonian magazine.

What are the factual errors on this leaflet so I may stand corrected? This incident is particularly relevant to the new proposed guidelines because it involves the honesty of researchers and the responsibility and credibility of the Biosafety Committee that was suppose to over-

view recombinant DNA research here in San Francisco.

What in the new guidelines will prevent this incident from happening again? What if any sanctions were taken against the people involved in the incident at UCSF?

Thank you for providing the opportunity for me to ask questions.

Yours truly,

Joel A. Ventresca

Joel A. Ventresca

ELI LILLY AND COMPANY

INDIANAPOLIS, INDIANA 46206

C. W. PETTINGA, Ph D.
EXECUTIVE VICE PRESIDENT

September 22, 1978

Dr. Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, Maryland 20014

Re: Recombinant DNA Research, Proposed Revised Guidelines, 43 Fed. Reg. 33042-33178 (July 28, 1978)

Dear Dr. Fredrickson:

In accordance with your letter dated July 19, 1978, and the above notice, we are submitting the following comments on behalf of Eli Lilly and Company concerning the Proposed Revised Guidelines for Recombinant DNA Research. Lilly is engaged in the research, development, production, and distribution of pharmaceutical, agricultural, and other products. It has extensive research and development facilities and its programs include research involving recombinant DNA.

(1) I-D-6. 10-Liter Limit on Volume.

Recombinant DNA technology is progressing rapidly from a laboratory phenomenon to developmental activities. The necessity for conducting scale-up experiments (greater than 10-liter volumes) is imminent. We do not see any unusual biological or containment hazards in association with larger volume experiments. Our laboratories as well as other industrial research groups have had extensive experience in the handling of highly toxic bacterial and viral pathogens and hazardous chemicals. For example, live polio virus, L-asparaginase-producing strains of *E. coli*, various pneumococci, insulin, alkaloids, synthetic hormones, and barbiturates have all been safely processed in volumes of thousands of gallons over periods of many years. With careful attention to development and production process design, we have encountered minimal safety problems. We feel that Lilly should act on the basis of our established expertise within the context of the proposed revised guidelines. As indicated in paragraph 2 below, we recommend that a mechanism be established for Lilly and other companies to share information with NIH (as it does with the scientific community) in a manner

that will foster the dissemination of new knowledge, yet protect the company's proprietary interests. We would consider these concepts equally important for academic laboratories.

(2) IV.-C.-2. Voluntary Registration and Certification.

The proposed guidelines provide that institutions not required to comply with the guidelines may nevertheless register recombinant DNA research projects with NIH by submitting the appropriate information to ORDA. Further, the proposals provide that NIH will accept requests for certification of host vector systems by the institution and that the submitter must agree to abide by the physical and biological containment standards of the NIH guidelines.

It is our understanding that a number of research institutions not subject to the guidelines (including ours) support them in principle and abide by the physical and biological containment standards delineated therein.

We recommend that the voluntary registration and certification procedures be extended to provide for sufficient latitude to encourage the voluntary identification of facilities engaged in recombinant DNA research and to provide NIH with information on private research laboratory and industrial research recombinant DNA efforts. This should be accomplished without subjecting the participants to a possible loss of confidential information and consequent competitive disadvantages through Freedom of Information requests. It would appear desirable for NIH to encourage the voluntary identification of facilities engaged in recombinant DNA research, the identification of senior scientists responsible for such activities within private academic and industrial research laboratories and the acquisition of information by NIH on the type of physical containment at these facilities.

The revised guidelines should expressly provide the opportunity for identification to NIH of facilities and projects at the discretion of the private industrial concern and for the ensuing dialogue which can occur regarding the scientific characteristics of such work. Under these procedures, we would not contemplate that NIH's role would require approval of projects or facilities in a regulatory sense. We perceive, however, that public interest can be

better served if private laboratories share with NIH information on their laboratory capabilities. Further, scientists within private research facilities, government, and industry should have enhanced opportunities for dialogue with the consequent assurance that recombinant DNA procedures are conducted in a safe and appropriate manner.

(3) IV-A-2. Institutional Biosafety Committee.
We believe that it is philosophically inconsistent to require that one or more members of the Institutional Biosafety Committee (IBC) shall not be affiliated with the institution. Since there has been no demonstrated harmful product in the five years following the first questions raised about possible hazards (cf. Comments on the Proposed Guidelines, Federal Register, July 28, 1978, p. 33044), there is no need to imply the existence of a hazard not being dealt with by the committees on the basis of their present composition. Individual laboratories should have the option of securing one or more non-affiliated committee members, but the inclusion of such individuals should not be mandated. Whenever members are appointed from outside the institution, their qualifications should be appropriate to enable them to examine, analyze, and interpret the problems associated with the experimental protocols and facilities being reviewed.

(4) II-B-3-C-(7). Exhaust Air Disposal.
In earlier correspondence concerning the design and construction of one of our P3 laboratory facilities, we described an air disposal problem and our method of solving it (letter to Dr. W. Emmett Barkley, March 14, 1978, copy attached). The Proposed Revised Guidelines do not address the possibility of recirculating treated exhaust air from a P3 laboratory to other parts of the building; we feel that this can be safely done and recommend including this alternative in the manner indicated in our letter. Dr. Barkley indicated his agreement with this extension of the guidelines in previous discussions.

(5) III-A-a-(1) and III-A-2-a-(1)-(b)-(1)-(c).
Eukaryotic DNA Recombinants.
The containment requirement of P2-EK2 for experiments with eukaryotic DNA of primates without the option of P3-EK1 seems inconsistent with the existence of that option

for the handling of whole genomes of transforming viruses. It is recommended that the P3-EK1 alternative be allowed for section III-A-a-(1). There is no reason to believe that experiments with primate DNA would be any more hazardous than the handling of the genomic DNA of a known tumorigenic virus.

(6) V. Footnote 1. Classification of Organisms.
Apparently, there is not yet an updated "Classification of Etiologic Agents on the Basis of Hazard" available; we retain our concern, expressed earlier, for the misclassification of various actinomycetes. We recommend that the members of this order which are pathogens be retained in Class 2 with all other thereby being Class 1. The commercial importance of several non-pathogenic organisms in this group would seem to warrant particular attention to this distinction.

(7) II-C. Shipment of Materials.
With regard to shipment of organisms containing recombinant DNA, provision should be made to exempt well-characterized non-hazardous clones from these regulations. Indiscriminate, strict regulation of the shipment of all organisms containing recombinant DNA is inconsistent with the general relaxation of containment requirements for certain experiments.

The proposed revisions will, in general, do much to stimulate needed research in this area. Of particular importance are the added opportunities to assess more completely questions of safety and the means to further minimize risks. We indorse the philosophy of the revisions in moving toward relaxation of constraints in the absence of evidence for hazards in the conduct of various recombinant experiments. The rational continuation of this process should ultimately lead to a state of knowledge commensurate to that which the scientific community recognizes in other types of life science research for which official guidelines are not required.

Sincerely yours,

C. W. Pettinga

[Enclosure included letter from Max M. Marsh, Lilly Research Laboratories, to Dr. W. Emmett Barkley, National Cancer Institute, March 14, 1978.]

rl
Attachment

UNITED STATES DEPARTMENT OF COMMERCE
The Assistant Secretary for Science and Technology
Washington, D.C. 20230
(202) 377-3111

SEP 22 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

I have reviewed the Proposed Revised Guidelines to control recombinant DNA research funded by the National Institutes of Health (NIH), as published in the Federal Register on Friday, July 28, 1978 (43 FR 33042), and offer the following comments for your consideration.

In the light of the development over the last two or three years of host-vector systems which cannot survive outside of carefully controlled laboratory conditions, and of the shifts in general scientific opinion based on increased knowledge about risks and benefits of recombinant DNA activities, I welcome the move toward guidelines somewhat less restrictive than those published in 1976. As you have pointed out (43 FR 33044, column 1, paragraph 1), ". . .no evidence has come to light of a product created by these techniques that has been harmful to man or the environment."

I am very much in favor of the opportunity which would be provided under Section IV-C-2 for voluntary registration of projects by institutions not required to comply with the guidelines and certification of host-vector systems proposed by such institutions.

In the "Decision of the Director," at 43 FR 33066, it is indicated that NIH was urged to provide the private sector, along with registration and certification, advice on interpretation of the guidelines and on the operation of institutional biosafety committees. We note that Section IV-B-3-a. Would require that the NIH Office of Recombinant DNA Activities (ORDA) "provide advice to all within and outside NIH, including institutions. . ."

(emphasis added). Further, Section IV-B-3-a(3) would require ORDA to make interpretations of the guidelines. We recommend that the guidelines explicitly provide for ORDA to advise voluntary private sector participants on biosafety committee operations, as well as interpretations of the guidelines, which advice we understand is now routinely available from ORDA.

Under Section IV-C-3 of the proposed guidelines, protection of confidential or proprietary information would be provided for. However, I am not certain that such information, whether in the hands of the Department of Health, Education and Welfare or of a local or institutional biosafety committee, can be satisfactorily safeguarded under existing statutes (e.g., 18 U.S.C. 1905 or 5 U.S.C. 552(b)(4)). I recommend, therefore, that a mechanism for protection of proprietary or confidential information be set forth in Section IV-C-3 in order to provide the private sector participants under the voluntary registration and certification program with greater assurance that their interests will not be jeopardized by the required disclosure for registration and certification. Specifically, I recommend that Section IV-C-3-a be amended by adding at the end the following:

> Any institution voluntarily applying for registration and certification under Section IV-C-2 which has identified confidential or proprietary information submitted to NIH is entitled, pending release of such information under subsections IV-C-3-a-(1) through (4):
>
> (a) to receive written notice from NIH of the proposed release;
>
> (b) to have the opportunity to request consultation with NIH regarding the appropriateness of the proposed release within 30 days of receipt of such notice; and
>
> (c) to withdraw its application within 30 days following receipt of written notification of a decision by NIH to release confidential or proprietary information. In such case, NIH shall

not release the information and shall return the application and all supporting material to the applicant.

Also, I recommend exploring the possibility of limiting the information required for registration to that absolutely necessary for the protection of public health and safety. Under Appendix C, Section IV-D-6, there would be required a description of each project, including information on the sources of DNA, nature of inserted DNA sequences, and the host-vector systems being used. I feel that there is the possibility of unnecessary disclosure of proprietary information and, therefore, a resulting reluctance on the part of some otherwise willing participants in the voluntary program to apply for registration and certification.

I appreciate having had the opportunity to comment on the Proposed Revised Guidelines and hope that these observations and recommendations may be of assistance to you.

Sincerely,

Jordan J. Baruch

P.S.

Don -
Jim talked over the Academy / RAC with Sid Galler. It looks feasible. If you or one of your people would like to explore it further give me (377-3111) or Sid (377-4336) a call.

Best
Jordan

MEMORIAL SLOAN-KETTERING CANCER CENTER

1275 YORK AVENUE, NEW YORK, NEW YORK 10021

Dr. Donald S. Fredrickson
Director of
National Institute of Health
Building 1 room 124
900 Rockville Pike
Bethesda, Md. 20014

NYC, September 22, 1978

Dear Dr. Fredrickson,

I have read the revised guidelines for DNA recombinant research and wish to express you my support and deepest appreciation. I fully agree that DNA recombinant research, like many other Promethean activities of the modern scientist should continue to be matter of everybody's concern. On the other hand, to insist on the old guidelines after the recent acquisition of data on the subject here and abroad would be a dangerous obscurantism which could be labeled, without exageration, the greatest threat to biology since the Lysenko affair.

Needless to say, that as a medical man who has been involved in the study of Man's inheritance for over 25 years, I look at DNA recombinant technology as the long awaited tool which may eventually permit a true hypocratic approach in medical genetics, i.e. the correction of genetic defects rather than the elimination of their carriers. This "Euphenical" measure (the term is Joshua Lederberg's) as opposed to currently used "Eugenical" interventions - abortion or sterilization of the unfit, selective mating, artificial insemination etc.- need not be inheritable. It should preferentially be limited to the somatic cells of a diseased tissue or organ for the sole purpose of adjusting the individual organism to its ecological environment when it happens not to be so because of its unfavorable genetic make up.

Sincerely yours,

Marcello Siniscalco

Marcello Siniscalco, M.D.
Member and Professor of Biology

[A-279]

MS/mw

MEMORIAL HOSPITAL FOR CANCER AND ALLIED DISEASES
SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
SLOAN-KETTERING DIVISION, GRADUATE SCHOOL OF MEDICAL SCIENCES, CORNELL UNIVERSITY

THOMAS J. BLESSING
DRAIN COMMISSIONER
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AREA CODE 313
TELEPHONE 994-2525

September 22, 1978

Donald S. Fredrickson, Director
National Institutes of Health
Bethesda, MD 20014

Dear Mr. Fredrickson:

I have enclosed one copy of the following:

1. Prepared testimony presented to the HEW hearings on the Proposed Revised Guidelines.

2. Resolution of the Ann Arbor, Michigan Democratic Party regarding recombinant DNA research.

In previous proceedings, a resolution of the Washtenaw County, Michigan Democratic Party regarding recombinant DNA research was entered into the record.

An examination of the resolutions clearly supports the contention of my testimony that there is not "overwhelming sentiment" for relaxation of the present guidelines.

There is absolutely no pressing public concern that would call for relaxation of the guidelines. Even proponents of unfettered research have spoken of new "breakthroughs coming at a dizzying pace". The existing guidelines have not prevented scientific advance. To relax the guidelines would be ignoring the many portential problems with recombinants. The risk is simply not worth the very small gain for a few scientists.

Please consider withdrawing the proposed revisions or at a minimum, rewrite the revisions.

I ask that these enclosures and this cover letter be entered as part of the comments relating to the proposed revised guidelines.

Sincerely,

Thomas J. Blessing
Drain Commissioner

rah

enc.

[Testimony printed with written statements submitted by witnesses at HEW public hearing.]

Office Open Week Days From 8:30 A.M. to 5 P.M.

ANN ARBOR DEMOCRATIC PARTY

RECOMBINANT DNA RESEARCH - PLATFORM STATEMENT

APRIL, 1978

In 1974, in an unprecedented move, leading biological scientists called for a moratorium on the use of new experimental procedures known as recombinant DNA research techniques. Using these procedures, the genes of plant, animal or bacterial species can be spliced together with the genes of an unrelated species and inserted into a host organism (usually al bacterium) which then can continue to grow and reproduce. The properties, both good and bad, of the organism which is thus created cannot be predicted in advance with certainty. Due to concern for possible hazardous effects, the National Institutes of Health (NIH) wrote and adopted guidelines to regulate research funded by the NIH. These guidelines govern the research that is performed at the University of Michigan. However, private laboratories capable of doing this research are not governed by the NIH guidelines. Debate continues within the scientific community concerning the hazards of recombinant DNA research and significant disagreement exists over its safety.

It is the responsiblility of the Ann Arbor City Council to ensure the health, welfare and safety of its citizens. To fulfill this responsibility, the Ann Arbor Democrats believe that private and public recombinant DNA research should be subject to local review and approval. Democrats believe that Council should actively demand a review role in the University's decision-making on this issue. Further, Democrats believe that an ordinance must be enacted to place private laboratories under the same strictures as the University laboratories.

72 Jane Street
New York N Y 10014
(212) 675-7173

Coalition for Responsible Genetic Research

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Membership Secretary

Francine R. Simring
Executive Director

September 22, 1978

Dr. Donald Fredrickson
Director
National Institutes of HEalth
Bethesda, Md. 20014

Dear Dr. Fredrickson:

Enclosed herewith are the comments of our organization on proposed revisions of the guidelines for recombinant DNA research as published in the Federal Register, July 28, 1978. A detailed technical analysis of the experimentation will follow under separate cover.

We trust that careful perusal by you, Secretary Califano, Mr. Peter Le Bassi, Dr. Henry Aaron, Dr. Julian Richmond, et al. of the many points we make in the public health interest will result in their incorporation into the guidelines and will help formulate the structures and procedures for impartial regulation of recombinant DNA activities.

We wish at this time to urge once more that <u>any revisions that weaken the guidelines be post-poned pending risk assessment data upon which such revision should be based</u>. At the present time such materials are not available.

With thanks for your kind consideration in this salient public matter,

Yours very truly,

Francine Robinson Simring

Francine Robinson Simring
Executive Director

FRS:fh

cc: Le Bassi, Aaron, Richmond
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COMMENTS ON PROPOSED REVISED GUIDELINES FOR

RECOMBINANT DNA RESEARCH

FEDERAL REGISTER, JULY 28, 1978

PART IV

INTRODUCTION

To date, the bulk of recombinant DNA research has been funded by government agencies and has been carried out on a small scale. However, the character of a significant proportion of the work is likely to change if commercial interest in the field continues to expand:

1. A goodly proportion of recombinant DNA activities will not be subject to the sanction of withdrawal of government funding (at present, one of the main mechanisms for control).

2. There will be growing pressure to scale up culture volume and to release organisms containing recombinant DNA into the environment in preparation for commercial application.

As the guidelines acknowledge, social considerations will contribute to decisions in those areas (p. 33070, Col. 1).

Therefore, the present review of the proposed revised guidelines by the Department of Health, Education, and Welfare is particularly well-timed for consideration of changes to ameliorate the following problems:

- the partisan structure of the NIH Recombinant DNA Advisory Committee
- the potential conflicts of interest implicit in regulation by the NIH whose function is to promote and fund
- lack of apparatus for effective treatment of social and regulatory questions posed by recombinant DNA activities

- primary responsibility for compliance to be transferred to local biohazard committeess
- the haste to lower standards of containment through revisions of the guidelines without experimental data to justify such revisions

The following comments address the need for structural and procedural changes.

I. *Structure of the NIH REcombinant DNA Advisory Committee (RAC)*

The RAC was originally established and defined to treat technical questions arising in connection with research funded by NIH (Federal Register 39, November 6, 1974, p. 39306). As presently constituted, it is not well-equipped to address questions of management and control. Nor is it sufficiently representative of the sectors that will be affected by recombinant DNA technology to address questions concerning the social good. Two courses of action are open:

Either: the committee remains as a technical committee, in which case another committee would need to be designed to examine non-technical questions.

Or: the committee should be reconstituted in order to deal more effectively and in a representative fashion with the broader issues of social responsibility and control.

The second alternative will probably be seen as more desirable, in terms of efficiency. In addition, a viable model for the second alternative already exists: in Great Britain, responsibility for screening all recombinant DNA activities has been assumed by a broadly representative committee, the Genetic Manipulation Advisory Group (GMAG). The GMAG advises the Health and Safety Commission which regulates recombinant DNA work under the Health and Safety at Work Act of 1974. The GMAG convenes subcommittees to deal with technical questions, but its membership is not predominantly technical.

RECOMMENDATIONS:

1. RAC Committee: The committee should be redesigned to be advisory to DHEW rather than to NIH. Final decisions on control and management should be made by an office of HEW which is not involved in promoting recombinant DNA activities.

2. Chairperson: The chairperson for the committee should not have close ties with any sectors involved in recombinant DNA activities. Such partisans cannot function impartially as is required for the responsibilities attached to the chair.

3. Composition: The present committee is narrowly constituted as might befit a purely technical committee. Representation of fields other than technical fields is meager. All nominations have come from the NIH. The NIH foresees only "modest" expansion of membership "as needed for expertise" (p. 33051, Col. 1). The committee should be expanded to include representatives of unions representing technical workers in this field, representatives of public interest groups, and some individuals not aligned with specific sectors but with knowledge and experience in law, public policy, regulation of other technologies with broad social impact, and environmental protection. Members should be chosen in consultation with the agencies with potential regulatory jurisdiction in this area, namely, OSHA, EPA, CDC, and FDA.

II. *Proposed Transfer of Primary Responsibility for Compliance to Local Institutions (p. 33044, Col. 1)*

Thus far, controls on recombinant DNA research have been based largely on principles of self-regulation and peer review. Experience during the past year, at two prestigious schools, has shown that irresponsible or thoughtless actions do occur under this form of control. Yet the response of the NIH has been to propose to increase, rather than to balance, the responsibilities of local institutions by transfering primary responsibility for control to those institutions and their biohazard committees (p. 33084, Col. 2). Under the proposed revisions, biohazard committees would be responsible for insuring compliance with the guidelines, and for medical surveillance, training, and the formulation of emergency procedures. Yet the IBC's are required to have only token representation of non-professional laboratory personnel and persons not affiliated with the institution (one in each category).

RECOMMENDATIONS:

1. Central Review: The two-level review of recombinant DNA activities should continue. Review by local biohazard committees should be followed by the NIH Office of Recombinant DNA Activities (ORDA).* It has been claimed that review by ORDA entails great delays. This suggests either that the ORDA machinery is unnecessarily inefficient or that the number of requests is too great to be controlled effectively. The volume of recombinant DNA projects needs to be reviewed by a reconstituted advisory committee. Given the uncertainties that surround the biological implications of much of the work in this field, it is essential that the volume of work be kept within manageable limits.

2. Composition of Institutional Biohazards Committees (IBC's): IBC's should include substantial (not token) representation of non-professional laboratory personnel and local communities. Nominations of these persons should come directly from their constituencies and not from local institutions.

III. *Procedures for Waiving Prohibitions on Construction of Certain Recombinant DNA's, Large-Scale Experiments, and Deliberate Release into the Environment of Organisms Containing Recombinant DNA (p. 33070)*

According to the proposed revised guidelines, prohibitions can be waived, if approved by the Director, NIH, on recommendation of the advisory committee. It is noted that societal as well as scientific considerations enter into a waiver decision.

As noted above (I), the NIH and its advisory committee are not well-suited to make decisions on processes which clearly involve important ethical and political considerations. They should not be made by a predominantly technical body nor by a government agency involved in promoting the activity under consideration.

IV. *Certification of Facilities and Training of Recombinant DNA Personnel*

According to the proposed revised guidelines, the IBC's will be responsible for review and approval of facilities and for training of recombinant DNA personnel. No standards, or qualifications for judging stand-

* Approval should not be given to experiments until both laboratories and workers in laboratories have been certified: see IV, above.

ards, are specified. Biohazards officers are only required for institutions with P3 and P4 facilities. This arrangement allows considerable scope for error, especially at smaller institutions where conceivably no staff person would be qualified to make an independent judgment on training and degree of physical containment.

RECOMMENDATION: Facilities, and the training of laboratory workers in those facilities should be certified prior to commencement of work involving experiments covered by the guidelines. Each institution should have a biohazards officer responsible for the certification process, who would report to the biohazards committee. A central registry of facilities and workers in those facilities should be maintained.

V. *Labelling of Organisms, Monitoring, and Legal Liability*

The proposed revised guidelines mention medical surveillance (33065, Col. 2; 33084, Col. 3) but the nature and extent of medical surveillance appears to be left entirely to the discretion of individual institutions. No provision is made for a central clearing house for keeping records of personnel, accidents, incidence of illness, or the degree to which organisms containing recombinant DNA are being contained. This means that there will be great difficulty in establishing legal liability in cases where illness appears to be linked to recombinant DNA activities. A general policy question which should be addressed is whether it is justifiable for any potentially hazardous activity to continue until an effective surveillance system has been articulated in relation to the legal system.

RECOMMENDATION: Effective techniques for monitoring recombinant DNA and the organisms containing it need to be developed. A biohazards officer should be appointed for each institution and should be responsible for monitoring, medical surveillance, and for keeping records. A central office (possibly within CDC, NIOSH, or EPA) needs to be established to maintain accurate records of personnel working with recombinant DNA, the incidence and severity of work-related illness, and of the escape of organisms containing recombinant DNA from physical containment.

VI. *Emergency Procedures and Cleanup of Spills*

According to the proposed revised guidelines, the IBC's will be responsible for reviewing and approving emergency plans for accidental spills and personal contamination (p. 33085, Col 2). The development of detailed emergency procedures is not required.

RECOMMENDATION: Detailed emergency procedures, which take into account the organisms being worked with, should be drawn up by the biohazards officer in conjunction with the local biohazards committee. The plans should be submitted to the central agency responsible for keeping records of certification of laboratories and training of personnel, and medical and monitoring records.

VII. *Risk Assessment*

The guidelines do not spell out the relation between the risk assessment experiments for which contracts are being let by NIH and the responsibility of the NIH advisory committee (RAC) for determining the potential risks posed by specific procedures (p. 33086, Col. 2). In the past, this has often meant that the advisory committee has determined the level of potential risk of a particular procedure through discussion rather than through experiment. (For example, the level of risk posed by E. coli bacteria programmed to make rat growth hormone and rat insulin was determined by the RAC at its April, 1978 meeting on the basis of rule-of-thumb calculations, not on the basis of experiment). Because risk assessment experiments are not required to accompany innovations in the recombinant DNA field, knowledge of the full implications of the technology lags far behind developments in the field. Yet caution and scientific canon would seem to have been sidestepped, for example, unnecessarily,due to hastening of proposed revisions to the guidelines before obtaining the data of the Martin-Rowe risk assessment experimentation.

RECOMMENDATION: It is necessary that a comprehensive program of risk assessment be integrated into a general policy framework. Specifically, such a program should require that risk assessment keep pace with new developments and precede all larger-scale applications and precede all procedures potentially involving release of organisms containing recombinant DNA into the environment.

MARK A. CHATIGNY
15926 Via Toledo
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September 22, 1978

Dr. Donald Fredrickson
Director, National Institute of Health
Bethesda, Maryland 20014

Subject: Use of Asporogenous organisms for recombinant DNA Research.

Dear Dr. Frederickson:

It has come to my attention that there are RDNA studies in progress that employ microorganisms having a spore state. For example Bacillus Subitilus Var. Niger has been discussed.

This microorganism is ubiquitous in nature and can be found in almost any part of the world, including the dry valleys of the Antarctica. I do not know its ecological role but one would suspect that it does have a role to play and that although it may be an inevitable evolutionary condition it is a remarkably stable organism. It will survive and propogate in ecological niches of an astounding range. In the spore form, it may last for years or centuries.

If only for reasons that parallel our unwillingnes to unwittingly colonize the Moon or Mars, I respectfully suggest that the guidelines limit any RDNA work with Spore forming organisms to those mutants that are asporogenous.

I am a strong believer in biological and physical containment but I would not be satisfied that the probability of release to the environment of a hardy spore containing controlled genetic information would be zero. While I see no immediate hazard to man from the work in progress, I am aware that a very long term

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environmental effect is possible. Lack of knowledge of the effects activates my concern.

Sincerely,

Mark Chatigny

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September 22, 1978

Dr. Donald S. Fredrickson
Director, National Institutes of Health
Bethesda, MD 20014

Dear Dr. Frederickson:

I would like to endorse the procedures recommended for control of recombinant DNA and related research, as described in the Federal Register of July 28, 1978, beginning on page 33069 and as outlined in Table III (two sections), page 33079 and Table IV, page 33083.

Sincerely yours,

Robert B. Couch

Robert B. Couch, M. D.
Professor of Microbiology
& Immunology and Medicine

RBC:lfs

[A-291]

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September 22, 1978

Dr. Donald Fredrickson, Director
National Institutes of Health
Bethesda, Maryland 20016

Dear Dr. Fredrickson:

I have read and agree with the majority of the proposed changes in the Proposed Revised Guidelines for Recombinant DNA research. I feel that the proposed changes are quite justified by the very low likelihood of eucaryotic gene expression in E. coli, by the inability of such gene expression, if it did occur, to produce injurious effects, and by the inability of E. coli K-12 to colonize the human gastrointestinal tract.

I would suggest that the conditions for shotgun cloning of mammalian and bird DNA should be changed from P2-EK2 to P2-EK2 or P3-EK1. The same choice is allowed for experiments 6, 12, 13, 19, 25, 42 and 43 and it seems perfectly consistant that a similar combination be allowed here, i.e. increasing physical containment should permit a reduction in biological containment.

Sincerely yours,

David Mount

David W. Mount, Ph.D.
Associate Professor of
Microbiology

DWM:kb

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September 22, 1978

Secretary Joseph Califano
Department of Health, Education and
Welfare
200 Independence
Washington, D. C. 20201

Dear Secretary Califano:

Enclosed are the Natural Resources Defense Council's comments on the proposed revised Guidelines for Recombinant DNA Research (43 FR 33042, July 28, 1978). In them we raise the same questions about the scientific basis for the proposed revision and the effectiveness of the enforcement sections that we raised with you in our meeting last May. You and your staff may be interested to read a more detailed discussion of these issues.

We appreciate the attention that you have devoted to this issue and your decision to have members of HEW participate in the recent DNA hearings.

Sincerely,

Marcia J. Cleveland

Marcia J. Cleveland
Staff Attorney

MJC:sja
Enclosure

[Enclosure printed on page A-175.]

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September 22, 1978

Dr. Julius Richmond
Assistant Secretary for Health
Room 716G, Humphrey Building
200 Independence
Washington, D. C. 20201

Dear Dr. Richmond:

Enclosed are the Natural Resources Defense Council's comments on the proposed revised Guidelines for Recombinant DNA research (43 FR 33042, July 28, 1978). We hope that you will consider them in making your findings and recommendations based on the hearings held September 15, 1978.

Sincerely,

Louis Slesin
Louis Slesin

Marcia J. Cleveland
Marcia J. Cleveland

Natural Resources Defense Council
122 East 42nd Street
New York, N. Y. 10017

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Enclosure

[Enclosure printed on page A-175.]

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September 22, 1978

Mr. Joseph Califano
Secretary,
Department of Health Education & Welfare
Washington, D.C. 20460

Dear Mr. Califano:

Reaping the potential benefits of recombinant DNA technology clearly depends on the ability to contain the potential public health hazards. I find no substantial evidence or argument presented in the draft revised guidelines or supporting documents to justify the major weakening of containment proposed therein. I am particularly concerned over the lowering of containment for shotgun experiments with DNA from birds and mammals; the lowering of containment for cloning eukaryotic viral DNA; and the transfer of authority for lowering guidelines from the NIH to local, nonrepresentative, nonexpert, part-time committees, an extraordinary transfer of public federal functions to private bodies.

The draft Guidelines and supporting documents, though representing considerable labor and effort, are marred by four major failings;

A) The absence of the most relevant, observations which form the basis for the need for containment in the first place.

B) A major logical fallacy, pervading the entire set of documents, in which the ability to perform a set of experiments safely, is confused with the safety of the materials themselves.

C) Heavy reliance on unreferred, unpublished, unexamined reports of small appointed committees, meeting in private, in complete contradiction to the canons of scientific process, and governmental process.

D) Extraordinary selectivity in quotation, in which no arguments or data which lead to a tightening of the guidelines are presented nor referred to.

It is of the utmost importance that the Guidelines discuss explicity the dangers of introducing foreign sequences into strains other than K12, for example into known epidemic strains of coli. Otherwise an environment will be created in which wild strains will be substituted for disarmed strains. No one present at Falmouth, for example, maintained that the introduction of mammalian DNA sequences linked to antibiotic resistant plasmids, into wild strains of E. coli would not be a serious potential public health threat. Since there are presently no laws, regulations, or statues prohibiting such experiments, the RAC has primary responsibility for presenting this clearly and cogently. It has so far failed in this responsibility.

Elaboration:

A) The documents on numerous occasions quote Dr. Gorbach's personal letter to the effect that K12 is unlikely to be converted to a pathogen. There is no mention of the more serious concern, namely the transfer of foreign DNA to strains of E. coli which are already pathogens, and some of which are epidemic pathogens. In this case the concern is the conferring of additional deleterious properties on a strain that is already a problem. I present below data on the existing public health problem from E. coli infections. The absence of such material in the PRG leads me to doubt the credibility of the revised guidelines.

1) In the United States, strains of E. coli are the number one cause of community acquired infections which are serious enough to require hospitalization (Gangerosa, 1978; National Nosocomial Infections Study).

2) E. coli strains are the number one cause of hospital-acquired (nosocomial) infections in the United States. These infections are rarely gastroenteritis, but more often acute infections associated with the urinary tract, surgical wounds, pneumonia, and bacteremia (bloodstream infection). Stamm, Martin and Bennet (1978) have recently reviewed the incidence and character of gram negative nosocomial infections. To give a sense of the magnitude of the problem, I calculate from their data the incidence of some E. coli infections;

per year/U.S.

90,000 E. coli surgical wound infections, with 2,700 associated deaths.

40,000 E. coli pneumonia infections, with 10,000 associated deaths.

17,000 E. coli bloodstream infections, with 4,000 associated deaths.

Of course all of these patients were compromised in some way or another, for example by being subject to surgery, but then it is just such individuals who are the normal target of bacterial infections, and are the relevant population of concern.

It is important to note that hospitals are containment environments, in which all of the workforce is trained to control infections, generally far better than that of biochemistry graduate students. Furthermore, many cloning experiments will be done in hospital departments. Both the recent violations of the guidelines were in Medical schools (Charles Thomas, at Harvard, and Boyer at San Francisco).

3) Epidemic strains of E. coli are well known and are a major cause of diarrhea in children and adults. Concern over them has been increasing in recent years, particularly with respect to infections of infants (Sack, 1976).

4) Most bacterial infections are of compromised individuals. For example infants are deficient in Immunoglobulin M and in several components of the complement system, making them more susceptible to certain infections, for example E. coli meningitis (Wilfert, 1978). A substantial number of patients in U.S. Hospitals receive immunosuppresin therapy which makes them much more susceptible to infection. Simililarly the aged are often much more susceptible.

The Falmouth conference focused entirely on infection of healthy adults by K12 strains, an unrealistic and limited scenario. Even the results on transfer of genes was done in the absence of antibiotic therapy. However, in the real world the problem is clearly the danger in the presence of antibiotics - of selection for recombinant plasmids due to their carrying genes for antibiotic resistance. (Levins, 1977).

5) Pathogencity is not simply a property of an organism, but a relationship between a strain of organism and some particular host. The failure to shown increased pathogenicity in some particular host does not rule out increased pathogenicity.

Thus E. coli strains possesing the capsular antigen K1 are a major cause of meningitis among human neonates and infants. These infections have mortality rates from 40-80% (Glode et al, 1977). Those infants that survive the infection often suffer developmental or eurological abnormalities. These strains are notuncommon in adults, but are rarely associated with disease.

The introduction of a plasmid specifying potent mammalian hormones, for example, into meningitis strains of coli could very well increase either its pathogenicity or the actual damage done to the infected infant.

6) In numerous well studied cases the pathogencity of E. coli strains for a defined host is associated with the presence of a particular plasmid. The spread of antibiotic resistance due to plasmids has become a major international health problem, and needs no review here. Similarly the production of enterotoxins coded for by plasmid genes are well known to be major determinants of pathogencity. It is also known that certain plasmids specify proteins, such as the K88 antigen, which affects the binding of the cell to a host tissue. This is a critical determinant for diarrheal infection in piglets.

The recombinant DNA technology involves the introduction of foreign genes into these very plasmids which are already associated with increased pathogencity of E. coli strains. There is every reason to believe that producing a variety of foreign proteins in E. coli strains, would alter their interaction with human hosts, and that some of these altered interaction with human hosts, and that some of these altered interactions would be pathogenic. A well-defined model for one class of problems, the induction of autoimmune disease is described in the Falmouth proceedings (King, 1978).

The failure of the PRG to discuss this problem, at the very heart of what we know about pathogenicity, is incomprehensible to me on scientific or public health grounds. Either the composition of the RAC is inadequate to the task, or the pressures for relaxation of the guidelines have resulted in the production of a heavily biased document.

B) In the absence of a clear description of the nature of the hazards, we are treated instead to a continous repetition of the following logically fallacious and misleading argument: If we follow the guidelines in cloning experiments, there will be little risk; therefore there is little risk to cloning experiments; therefore we can relax the guidelines, which are unnecessary due to the lack of risk.

This is formally akin to arguing that since iodine^{125} can be handled safely, there is little risk associated with iodine^{125}; therefore we can relax the procedures for handling iodine^{125}.

For example, a sophisticated form of this argument appears on page 33044, first paragragh. It is argued that since harmful effects have not yet come to light, there is little support for the notion of inadvertantly creating hazardous organisms. This then is used as an argument to justify weakening the guidelines. But all the work done so far has been under the guidelines, if we are to believe the protestation of the RAC.

Thus the absence of adverse outcomes may reflect

i) the effectiveness of the current guidelines.
ii) the lack of any surveillance, monitoring, or even risk assessment program to look for adverse outcomes.
iii) failure to follow the guidelines, and true lack of hazard in the experiments. Lack of hazard cannot be determined, under conditions where proper guidelines are being followed.

Thus in no sense do the conclusions follow from the premise, even accepting the premise.

The logic that handling materials safely is equivalent to "the material is safe", will lead to the total breakdown of safe handling procedures.

C) Reliance on private reports.

The primary documents on which the PRG appears to be based are the Chairman's summary of the Falmouth meeting (it is clearly not based on the proceedings, which have substantial data supporting the need for containment and further study), an agricultural panel, and the so-called Ascot meeting.

The Falmouth meeting, though useful, was limited in scope. Its composition was by invitation from an organizing committee intimately associated with recombinant DNA research. The meeting was not announced to the scientific community. Scientists not invited, but who may have been in possession of useful experience or data, had no opportunity to present their views. The number of people invited was very small. The subject matter was limited to recombinant DNA research in K12 strains, despite the fact that no laws or statutes prevent people from cloning in any strain of interest. There was little discussion of nosocomial infections, of laboratory acquired infections, or of the problem of transfer of genes from K12 to wild strains outside the human gut. Nonetheless the Falmouth conference called for a whole series of risk assessment experiments, few of which have been done, and fewer reported on. Yet the PRG continuously fails to refer to this need for additional data.

The Ascot Conference

The revision of the guidelines downward for cloning of eukaryotic viral DNAs relies almost entirely on the "Report of the US-EMBO workshop to Assess Risks...." included as appendix E, page 33159 of the Federal Register. It is totally obscure to me what sector of the United States population, scientific or otherwise this group represented. One gets the impression that these scientists must have been representatives of the U.S. government. Yet there is no statement or announcement of who chose them or how they were chosen. In fact, they must have been an adhoc committee of individuals interested in changes in the guidelines, or else have been invited by EMBO. Either way they neither represented nor were accountable to any democratic body. Twenty seven scientists were in attendance, a remarkable small sampling. The group met in England, in private. The meeting was not announced to the virological or microbiological communities. In fact, they did not even notify the offical British body responsible for recombinant DNA policy, Gene Manipulation Advisory Group, of their meeting. The report was not published for comment in any scientific journal, even the Virology journals eg, Intervirology, J. Gen. Virology, J. Virology, Virology.

The International Congress of Virology met from August 30 - September 6 in Europe. Over 1,500 Virologists were in attendance from around the world.

No presentation of either the arguments or the conclusions was presented to this assemblage of the world's virologists in any workshop or meeting session. The existence of the report was not even announced in one of the plenary sessions.

Yet now we find that U.S. national policy is being made based on this report of 29 individuals chosen in part by people interested in revision of the guidelines. The scientists in attendance were eminent virologists whose opinion carries considerable weight. I found myself in agreement with many of their conclusions, though at sharp odds with certain major points absent from the report.

One of the most disturbing features is that the document reads far more like a position paper lobbying for one point of view, than an unbiased exploration of the possibilities. All possibilities of hazard, if brought up, are dismissed as "unlikely" "impossible to conceive" etc. One would never know from reading that most of the worlds virologists and bacteriologists study these organisms because certain of them are agents of human disease.

Despite the fact that all the individuals were completely well meaning, the overall mechanism was the same; a governmental committee, (RAC) supposed to be operating democratically, draws conclusions based on the finding of a private committee, meeting behind closed doors, representing a narrow sampling of a wide range of views.

A few examples of conclusions in the report open to question. The group "could not envisage a plausible risk set of circumstances whereby a risk to the community could develop". This is simply a statement about the limitations of a selected group of 27 virologists, not evidence about hazards. Thus the document concerns no discussion of the fact that some of the best described mechanisms for the generation of new viral pathogens is by rare recombinants between strains not normally reproducing in the same cells. Neither is there a substantial discussion of the role of defective particles in pathogenesis. Had their deliberations taken place before an open meeting of virologists, infectious disease, and public health personel, I believe the final document would have had a substantially different character.

The document "Implementation of the U.S. EMBO-EMBO report", page 33168 contains the extraordinary statement "The group felt that the only plausible way E. coli K12 could gain entry into laboratory workers was by oral ingestion". In fact the data on both laboratory acquired infection and hospital acquired infection, indicates that aerosols, cuts, syringe punctures, are primary routes of bacterial infection.

The entire document is concerned with the comparison of viral disease with viral-like disease from an E. coli containing viral sequences. But the report fails to deal with the problem of generating increased bacterial pathogencity from viral sequences. Is it really impossible to conceive that bacteria containg in their envelopes the viral proteins that permit viruses to attach to mammalian cells, might not have increased host range, colonizing ability, or pathogencity?

D) Selective Quotation.

The documents continually present only one side of the argument. Gorbach's letter on unlikelihood of converting K12 into an epidemic pathogen is continously referred to, without discussion of the fact that there was major concern of transfer of chimeric plasmids to wild strains of E. coli. There is no reference to the recent paper showing that EK2 strains cause death in healthy mice when administered intercranially, interperitoneally, or intravenously. (Levy, Sullivan and Gorbach, 1978).

Just one example of many, many such biased presentations; On page 33123 the Environmental Impact Assessment deals with the likelihood of transfer of DNA from coli K12 to wild strains by naturally occuring lambda bacteriophage. Since much of the cloning is done with lambda vectors, using cells sensitive to lambda phage, and containing lambda sequences, this is a serious possibility. According to the document "It (lambda) is considered very unlikely to survive and to infect resident E. coli in animals and humans, being highly sensitive to stomach acid, reluctant to infect smooth E. coli cells (the type normally found in the gut) and susceptible to drying, as would occur if it escaped into air". Later two personal communcations are referred to in support of this general position. Thus we are to believe that lambda bacteriophage which was originally isolated from nature; and E. coli K12, the host from which lambda was originally isolated from, are unlikely ever to find each other in the natural environment! Perhaps lambda doesn't survive in the human gut. What about sewers, urinary tracts, soil, and chicken guts, all friendly habitats for E. coli.

In conclusion, the proposed revisions of the guidelines are premature. They are not based on data or positions gathered under the normal canons of scientific investigation, modeling, and verification.

The benefits of recombinant DNA technology can be reaped perfectly efficiently under the existing guidelines. Neither pressure from commercial enterprises interested in exploiting the technology, nor over-eager scientists involved in the excitement of research, should be allowed to unduly influence the RAC. Their primary responsibility just be the protection of public and environmental health. The current proposed revisions are a step backwards from that responsibility.

Sincerely yours,

Jonathan King

Jonathan King
Associate Professor of Biology

JK:mcp
see references on
following page

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23 September 78

Donald S. Fredrickson, MD

Director, NIH
9000 Rockville Pike
Bethesda, MD 20014

Dear Dr. Fredrickson:

This letter is in response to the proposed revised guidelines as published in the Federal Register (July 28. 1978) and for which comments were solicited by September 27, 1978.

On February 1. 1977, I appeared before the Stanford University Administrative Panel on Recombinant DNA Research (the Biohazards Committee required by the NIH Guidelines) and read a statement regarding the general nature of the potential hazards connected with recombinant DNA research and with some specific matters as well. These matters were also covered widely in the local press at the time. In May, 1978 I appeared again before that committee and again raised some of the same points, but as of today no published response has been made by that committee.

Since some of these matters are of general interest and others of greater local interest they should be of interest to you in reviewing the proposed revisions. These points are:

1. The role of mistakes in scientific progress
2. The role of ignorance in scientific progress
3. Worker protection
4. Conflict of interest
5. Earthquakes

I will deal with the last, earthquakes, first so that there is no mistaking its importance or relevance.

5. EARTHQUAKES

I said in February 1977. "It is generally agreed that since there may be danger in recombinant research, there must be containment. But Stanford is in earthquake country. I need not elaborate upon that fact to this audience. But what will happen to all of the little games being played in P2 and P3 containment if there would be a great big shake? You can write your own scenario as well as I can. What frightens me is the attitude of the preeminent DNA scientists who live here at

Stanford. They certainly know about earthquakes - but they have never raised the seismic issue as a possible complicating danger. But there is nothing in the Guidelines, the draft Environmental Impact Statement or in the minutes of the Administrative Panel which addresses this question. And yet they consider themselves as persons who are concerned with safety!"

Since that statement was made, the Administrative Panel has made some tentative probings in that direction, but by their own admission to me in the May 1978 meeting it by no means deals with the problem in depth. Dr. David Hogness is one of your senior advisors. He is also a Stanford scientist. He listened to my comments in February 1977. Yet I still have not seen him take the lead - or in any other way - deal with this matter. If there have been activities by him or others which are not generally known I would greatly appreciate being directed towords them and , if need be, retract my criticism. And of course your office has also drawn upon the expertise of Drs Paul Berg and Stanly Cohen, eminent scientists who also seem to have ignored this issue.

The issue of containment remains an important one - although I believe it lies in the Maginot Line philosophy. But granting the validity of that approach nevertheless, it is important for your office to understand the thinking of people 3,000 miles away on this matter. School construction, hospital construction, emergency regulations of all sorts are all predicated on meeting earthquake standards. The thinking of many people frequently returns to this subject again and again. It is difficult to people living at a distance to comprehend the pervasive nature of this problem. But your own title includes the word "National" and puts the responsibility on your shoulders, the necessity of considering such local considerations - while in truth seismic disturbances do occur with regularity along the entire California coast - from Los Angeles to San Francisco.

1. MISTAKES

A fundamental premise of the workings of your office and of your Advisory Panels is that intelligence is put to work and mistakes are thereby avoided. That thinking is, in the main, true. But it is not entirely true. In February 1977, I stated,

"Mistakes do happen, and in truth must be expected in research. Santayanna said, "He who ignores history is condemned to repeat it". Let us review the origins of the two greatest advances in the therapy of infectious diseases - antibiotics and vaccines. Thye did NOT begin thru intelligent, planned experiments, thru serendipity or even thru accident. They resulted from mistakes - outright stupid mistakes. Fleming left his Petri dish uncovered and Pasteur let his culture go bad. If Fleming and Pasteur could make mistakes, then certainly the

eager beavers who want to do do this work today are also capable of making mistakes too. What about the Salk vaccine? After millions and millions of people were inoculated - including some in this audience - only later was it discovered that the Salk vaccine had been contaminated with a foreign virus, SV40. Fortunately, SV40 is not immediately lethal - it only produces cancers in animals - not yet in man. But under the Delaney amendement, it is against the law, against FDA regulations, to administer such carcinogens!"

I do not want you to draw the conclusion that I am anti-scientist or anti-experiments or even anti-acquisition of new knowledge. I am Clinical Professor of Anesthesia at Stanford University. I have been for many years a member of the American Physiological Society, the American Society of Pharmacology and Therapeutics, Sigma Xi , etc. But what I am saying is that, given the role of mistakes in other - and in this case - closely related science, it behooves you to proceed with utmost diligence. I know the arguments of Berg et al that their past record indicates that that is in fact their position. I disagree - in the sense that extreme care at one point in history is no license to proceed at a less careful pace at another point in history. The revised guidelines should reflect such extreme diligence.

2. IGNORANCE

Even the most well-intentioned people work in science without full knowledge of the entire situation, including its hazards - not because they choose to ignore those hazards or because they are knaves and do so deliberately. Often the knowledge simply does not exist at that given point in time. In February 1977 I stated:

"Then there is the danger of ignorance. Let us look at the Curies. Madam Marie Curie, twice a Nobel laureate. Irene Joliot-Curie, her daughter and a noted scientist in her own right, and then her son-in-law, the incomparable Frederic Joliot-Curie. These 3 people were certainly not stupid or foolish - by any standard. Yet they died of leukemia - because at the time of their exposure no one appreciated the biological dangers of radiation. Along similar lines and presaging the next point I will be making - I must consider the ethical and moral question of Stanford hiring people to work in the DNA labs. In this connection I can not set aside the memories burned into my conscience from my childhood in Passaic New Jersey where Women workers painted watch dials with radium tipped brushes which they licked to get the needed fine tip. They all died of radiation injury, some of them most horribly with cancers of the mouth. Yet, no one was to blame - the knowledge simple was not there at the time"

If one appreciates the role of ignorance as well as of mistakes, it behooves us again to proceed with utmost caution, to carry out the necessary experiments to test all of the reasonable hypotheses - and even some of the unreasonable ones, Dr. Fredrickson. We are not God - we are only puny mortals, dealing with lives of other puny mortals as well.

3. WORKER PROTECTION

In February 1977, I said "What do the Guidelines say about 'ensuring that research is carried out in accordance with the standards and procedures under the OSHA Act. This is an area of importance to local institutions but need not be included as a requirement in the Guidelines....I, (Fredrickson) would also encourage all institutions to review their insurance compensation programs to determine whether their lab personnell in the research area are covered for injuries."

"Importance is acknowledged, the existence of Federal and state laws is recognized, but despite suggestions to the contrary, they do not ask for compliance. We have been told repeatedly by Dr. Hogness and others that there is no real or significant risk. If that be true, then why waste valuable monies on insurance policies? Do you get informed consent from your laboraotry workers when they come on the job? Do you tell your technicians that even though you may think there is no risk, that nevertheless the NIH guidelines have urged you to make sure that there is enough insurance coverage "just in case"? You can depreciate your lab equiptment. You can, as it is said, "cost it out". But please, gentlemen, dont depreciate human life or cost out human suffering by the expedience of buying an insurance policy".

There have been developments in this area since my statement of 18 months ago. But without going into detail I think that they can be safely characterized as tentative , preliminary and inadequate.

4. CONFLICT OF INTEREST

This is an area of constant concern to you in all aspects of research supported by NIH. It is certainly not new. In February 1977, I stated:

" One can hardly argue with a scientist who is solely on the search for truth. But if a university scientist wants to get into the commercialization of recombinant research, then he cannot, at the same time, sit on committees which set the rules and give out the money for such research. A standard for conflict of interest should apply to all those who earn handsome consultant fees or who have invested their own monies in such commercial enterprises - and this includes everyone even Nobel laureates. This subject requires nothing less than full and complete disclosure of all outside connections. But nowhere in the Guidelines or in the deliberations of this panel has this important ethical question been addressed"

It is now September, 1978. From what I have read, the situation has remained unchanged. If I am wrong or ill-informed, I would greatly appreciate being corrected.

In addition to the comments I have made earlier, I should like to make some on the present guidelines revisions. I think that there should be greater adherence to NEPA and OSHA. The reversal of the submission of the Guidelines before the Environmental Impact Report is a clear violation of the law and was inexcusable when coming from a Federal official like yourself, Dr. Fredrickson. The role of local State Health agencies should not be overlooked and utilized to the fullest. This is not a matter of preemption, but simple utilization of the best resources and thinking. For example, the simple notification of the local biohazards committee and the NIH of accidents and/or violations (Sec 1V-A-4-h).

Others have made recommendations with which I heartily concur. The establishment of a central registry of "accidents" might help in the drawing up of future revisions - either upward or downward depending on life's own experiences. Particularly I am concerned by the lack of sufficent teeth and penalties in the sections dealing with non-compliance. Specifically there is the matter of worker compensation and more particulary the remedy of the situation which caused the difficulties in the first place. The history of occupational safety and health is replete with such deficencies, and it is not over with yet. And in this connection, I do not consider or put into a different category the Universities from private industry.

Sincerely,

M. Jack Frumin MD

M. Jack Frumin, MD
Clinical Professor of Anesthesia
Stanford U. School of Medicine

cc: Senator A. Cranston.
Rep Paul McCloskey
Prof J. Brauman
Prof B. Richter, NL

the University of Alabama in Birmingham / UNIVERSITY STATION / BIRMINGHAM, ALABAMA 35294

the Medical Center / DEPARTMENT OF MICROBIOLOGY / September 23, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Don:

I have read the Proposed Revised Guidelines for Recombinant DNA Research and accessory information as published in the Federal Register on July 28, 1978 (p.33042-33178). Overall I am impressed with the way NIH has considered all evidence, opinions and other relevant information in drafting a well organized, comprehensive and realistic set of Guidelines to allow the substantial benefits now arising from this research to be attained for the benefit of all. In arranging my comments on the Proposed Revisions of the Guidelines for Recombinant DNA Research, I decided to consider each section of the Guidelines in order of appearance and to intermix my comments of support for certain sections with those seeking clarification of apparent ambiguity as well as those dealing with several minor and two more substantial criticisms of the Guidelines as now proposed. These two more significant criticisms concern Appendix A which lists microorganisms that exchange genetic information and the levels of containment for some experiments involving cloning of eukaryotic viral DNA sequences in EK1 host-vector systems of Escherichia coli K-12.

My comments are as follows:

1. The basis for the conclusion that recombinant DNA research with the E. coli K-12 host-vector systems is much safer than originally believed and the means by which this conclusion was reached are presented in a complete and thorough manner in the Decision of the Director to Issue Revised Guidelines and in the Proposed Environmental Impact Statement. I agree with this conclusion that was initially stated in my letter to you of April 22, 1977 and which I have reiterated on numerous more recent occasions. However, in view of the substantial data to support this conclusion, I was somewhat bothered to read statements such as "....no evidence has come to light of a product created by these techniques that has been harmful to man or the environment" (p. 33044, Col. 1) with the implication that these negative results are indicative of the safety of recombinant DNA research. I have criticized the use of this particular argument in behalf of the safety issue in a paper presented June 6, 1978 at the Third International Symposium on the Genetics of Industrial Microorganisms in Madison, Wisconsin. A preprint copy of this paper, which will soon be published in ASM News as well as in the Proceedings of the Symposium, is attached as Appendix A to this letter. In it I state "The sixth factor [leading to the general belief that recombinant research with E. coli K-12 host-vector systems is safer than originally believed]

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has been the absence of any noticeable biohazard associated with the construction of any recombinant during the past several years. While reassuring, it should be noted that biohazards were not looked for and, indeed, all experiments were conducted under levels of physical and biological containment that we now agree were over-restrictive and which would preclude manifestation and/or detection of any biohazard should they have arisen. Thus it is scientifically invalid to use the experience of five years' research as a justification to argue that biohazards do not exist. It will thus be necessary to design and conduct experiments expressly for the purpose of determining whether the introduction of foreign DNA does or does not result in manifestation of biohazards and such experiments have not been done". I should hasten to add that such experiments have commenced but have not been fully reported. I would, therefore, prefer that you downgrade the importance of the above-cited argument for the safety of recombinant DNA research and rely instead on the substantial body of factual information and valid experimentation to substantiate the basis for the conclusion that recombinant DNA research with E. coli K-12 host-vectors is far safer than any of us had originally believed four years ago.

2. Section I. Scope of the Guidelines (p.33069-33070). The organization and clarity of this section has vastly improved over both the previous Guidelines and the draft arrived at by the RAC. I do, however, have some specific comments on Sections I-D Prohibitions and I-E Exemptions as described in the following four points.

3. Sections I-D-1 and I-D-2 (p.33070). Since VSV and moderate risk oncogenic viruses are or can be construed to be Class 3 agents, there is a paradox which, while dealt with in the Decision of the Director to Issue Revised Guidelines statement, still persists in the Revised Guidelines as now written. It should be stated explicitly in Section V, footnote 2 (p.33086) that the basis for allowing cloning of genetic information from VSV and moderate risk oncogenic viruses is the likely difficulty of faithful transcription and/or translation of this genetic information in prokaryotic host-vector systems, which would therefore be less likely to lead to a biohazardous condition than might cloning genetic information from Class 3 prokaryotic or lower eukaryotic organisms. I might add that I hope that, in the near future, NIH would thoroughly consider the basis for prohibitions I-D-1 and I-D-2 in light of the fact that recombinant DNA research with organisms in the Class 3 category as well as the deliberate cloning of genes specifying potent toxins can provide information not now available on the biochemical and genetic bases of pathogenicity of some of these agents and can also provide information that might lead to effective means of diagnosis, treatment and/or prevention of diseases caused by these agents. Such work is definitely in the national interest and means for its conduct and performance should be facilitated. I thus strongly believe that the lifting of these two prohibitions should not be decided solely on a case-by-case basis but rather should be based on a general consideration of the benefits and risks of any and all experiments in either of these two categories. The facts that the allowed cloning of genetic information from some Class 3 viral agents already constitutes an exception to Section I-D-1 and the existence of P4 containment and the eventual approval of EK3 host-vector systems whose uses are not stipulated for any experiments in the Proposed Revised Guidelines should serve to justify

reconsideration of all experiments now prohibited under Sections I-D-1 and I-D-2.

4. Section I-D-3. (p.33070). I do not understand why this prohibition is restricted to the "deliberate creation ....of a plant pathogen with increased virulence and host range" and does not also include such amnipulations concerned with animal pathogens.

5. Section I-E. Exemptions (p.33070, Col. 2). This entire Section is a very necessary and worthwhile addition to the Guidelines and Section I-E-5 certainly provides flexibility for making exemptions other than those now allowed pending adequate review and public input on potential recombinant DNA experiments or uses that pose little or no risk to public health or the environment. On the other hand, as mentioned below, I have specific criticisms about Section I-E-4 as now proposed which constitute one of the two major criticisms I have about the Proposed Revised Guidelines.

6. I will consider together my criticisms of Section I-E-4 (p.33070, Col. 2), Section III-A-1-b-(1) (p.33077, Col. 2), Section V-footnote 35 (p.33088, Col. 2), Appendix A (p.33089) and Appendix D to the Proposed Environmental Impact Statement (p.33158-33159).

The information provided to you by the RAC and others that led to the listing of organisms in Appendix A seems to have been misleading, inaccurate and incomplete and thus the statement on page 33044 "a list of donor-host pairs to be exempted... is a conservative one, restricted to pairs of organisms for which there is documented evidence of natural exchange" is false. In reviewing the information which is now in Appendix A to the Revised Guidelines and Appendix D to the Proposed Environmental Impact Statement (p.33158-33159) this past July, I wrote a lengthy letter to Drs. John Spizizen and Donald Helinski raising numerous issues pertaining to these lists. A copy of my letter to Drs. Spizizen and Helinski which was not dealt with in a substantial way at the August, 1978 Meeting of the RAC is attached to this letter as Appendix B. I will enumerate the problems as follows:

a. The first problem concerns the absence of the specific criteria used to include or exclude groups of organisms from Appendix A. In footnote 35, Section V (p.33088, Col. 2), it defines genetic exchange "as observable under optimal laboratory conditions by transformation, transduction, phage infection, and/or conjugation with transfer of phage, plasmid, and/or chromosomal genetic information." and then goes on to state, "Note that this definition of exchange may be less stringent than that applied to exempt organisms under Section I-E-4." The difficulty arises in that nowhere in the Guidelines, whether in Section I-E-4 (p.33070, Col. 2) or in Appendix A (p.33089) or in Appendix D of the Proposed Environmental Impact Statement (p.33158-33159), are these more stringent standards for demonstration of exchange by natural physiological processes given. It is evident from the list of microorganisms in Appendix A and the existence of Section III-A-1-b-(1) (p.33077, Col. 2) that a more stringent set of standards for demonstrating exchange by natural physiological processes was sometimes but not always used. I should note that if the definition

of genetic exchange as used in the Current Guidelines for Recombinant DNA Research were employed, then one list of exchangers would include any and all gram-negative microorganisms (see Appendix B to this letter). If, on the other hand, the criterion of genetic exchange by natural physiological processes is restricted to a demonstration of stable inheritance and expression of chromosomally transferred and integrated genetic material, which was alluded to as the definition being employed during discussions of this issue at the August, 1978 RAC Committee Meeting, then inclusion of all the organisms listed in Appendix A is unjustified (see Appendix B to this letter).

In establishing criteria and delineating the evidence necessary to list an organism or group of organisms in Appendix A, I think it realistic that relatedness be based on demonstration of genetic exchange and/or by demonstration of ∿ 30-40% DNA sequence homology as revealed by DNA reassociation kinetics under stringent conditions. The necessity for demonstration of exchange by conjugation, transduction, or transformation is often a haphazard circumstance influenced by luck in the choice of strains, phages and/or growth conditions. It thus seems logical that use of current knowledge and techniques of molecular genetics to obtain information on relatedness should be permitted.

The basic idea for the exclusion stated in Section I-E-4 was due to the fact that recombinants formed in the laboratory by recombinant DNA technology between organisms that exchange DNA naturally would not be novel. The issue of safety was secondary. However, the safety issue has apparently been used to exclude some but not all organisms listed in Appendix D of the Proposed Environmental Impact Statement (p.33158) from the list of organisms in Appendix A of the Proposed Revised Guidelines (p.33089). In addition, the safety issue has been used inconsistently since those species of Bordetella, Pasteurella, Yersinia, Neisseria, etc. that are animal pathogens and which have been demonstrated to exchange plasmids, at least, with E. coli are excluded whereas all species of Pseudomonas and Erwinia, many of which are plant pathogens and many of which have not been demonstrated to exchange genetic information with E. coli, are included in Appendix A. I realize that NIH has greatest familiarity and responsibility for the public health of humans, but I should reiterate what I have often said that the human species is dependent upon plants, not the other way around. Thus while I am not totally opposed to the issue of safety being used to omit certain organisms from lists to be included in Appendix A, I do believe that the basis for such decisions should be stated and appropriate consideration to the safety of all important higher organisms should be given.

b. The next problem concerns the taxonomic relatedness and evidence for genetic exchange among the organisms listed in Appendix A (p.33089). Since I am not an expert on bacterial taxonomy, I have relied on Bergey's Manual of Determinative Bacteriology (8th edition) and the guanine-cyto-

sine contents of DNA in microorganisms as listed in the Handbook of Microbiology (Vol. II, p.585 and following) to provide some guidance. Since Appendix A lists bacterial genera on the list of exchangers with the exception of a few microorganisms that are also designated by species names, I list in Appendix C to this letter the ranges of DNA guanine-cytosine contents of the species within these genera as an indication of the potential relatedness among the microorganisms both within and between these various genera. As has been pointed out by others, there is DNA sequence homology and evidence of exchange of chromosomal genetic information among all members of the genera Escherichia, Shigella, Salmonella, Arizona, Citrobacter, Enterobacter, and Klebsiella, although the evidence for chromosomal gene exchange and degree of DNA sequence homology between either Klebsiella or Enterobacter and other members of the group are less substantial or convincing than evidence for the close relatedness among Escherichia, Citrobacter, Salmonella and Shigella. On the other hand, there are wide differences in DNA guanine-cytosine contents among the species that constitute the genera Serratia and Erwinia (including Pectobacterium) and although there is evidence for some Erwinia species of genetic exchange with Escherichia coli K-12, there are little or no data on exchange for most species in either of these genera. There is also inadequate DNA sequence homology and no data on chromosomal genetic exchange between either Serratia or Erwinia and members of the Enterobacteriaceae other than Escherichia coli.

The situation is worse in terms of the Pseudomonas species since guanine-cytosine contents vary from a low of 48% up to 69% and while there is evidence for chromosomal transfer using Inc P1 plasmids from only three or four species of Pseudomonas to Escherichia coli, no such evidence exists for any of the other species of Pseudomonas and certainly none with regard to genetic exchange between Pseudomonas species and other members of the Enterobacteriaceae such as Salmonella, Shigella, etc. One can make additional criticisms based on the information included in Appendix C to this letter but the available information really needs to be examined by an appropriately constituted panel of impartial experts.

c. Another problem concerns the issue of whether data are available on reciprocity of exchange. For example, although there is evidence for transfer and inheritance of chromosomal information from Pseudomonas aeruginosa to E. coli K-12, I don't believe that the reciprocal experiment has been done. In any event, numerous other examples could be given since most studies have demonstrated transfer and inheritance to E. coli K-12 and not from E. coli. I believe it is logical to assume that if chromosomal material can be transferred and inherited in one direction that it could be inherited in the opposite direction. This assumption of reciprocity in the absence of data proving reciprocity should, however, be clearly stated.

d. Another problem not considered concerns the fact that the exclusion granted in Section I-E-4 allows one to clone, for example, Salmonella DNA into Pseudomonas or vice versa even though there are no data to indicate that Salmonella species can exchange chromosomal genetic information with Pseudomonas species. In other words, the list of organisms in Appendix A (p.33089) is based almost entirely on the ability of organisms on the list to transfer chromosomal information to E. coli K-12. Thus, if it is the intent to conclude that if both organisms A and B can exchange chromosomal information with organism C that exchange between organisms A and B would occur even though this had not been demonstrated, this should be explicitly stated. I might add that such an assumption becomes somewhat farfetched when one considers that Acinetobacter calcoaceticus has a DNA guanine-cytosine content of 42-43% and another organism listed in Appendix A, Rhodopseudomonas sphaeroides, has a DNA guanine-cytosine content of 71%.

e. Another problem with Appendix A is that it is incomplete. Lists of exchangers in the genera Bacillus, Streptococcus, Haemophilus and Streptomyces are lacking and these omissions will impede recombinant DNA research with these organisms and also the development of new host-vector systems. This is also bothersome since although it is now possible, for example, to clone Bacillus pumilis DNA in B. subtilis, the Proposed Revised Guidelines prohibit such an experiment until such time as the RAC approves certain B. subtilis derivatives as HV1 or resolves the problem in some other way.

7. Section II. Containment (p.33070-33076). Overall, this section is extremely well done. I very much support the idea of alternate practices of achieving physical containment at the P3 and P4 level and believe that the Laboratory Safety Monograph is extremely well done and will be most helpful and an important improvement over Appendix D of the Current NIH Guidelines. I do, however, have some minor points as enumerated below.

8. Section II-B-2-a-(13). dealing with laboratory gowns, coats or uniforms (p. 33072). Although it should be obvious that laboratory clothing is designed to protect undergarments from contamination with biological materials and that investigators wearing such protective clothing are most likely to experience aerosolized or spilled materials on their fronts, I have noted in laboratories that I have visited as well as in my own laboratory that investigators have a tendency to leave such laboratory coats open. I thus think it might be helpful to be more explicit in this section and to state that such laboratory gowns, coats or uniforms, etc. should be buttoned, zippered, etc.

9. Section II-B-2-b. Containment Equipment (p.33072). The use and necessity of biological safety cabinets in P2 laboratories is ambiguous. This section refers to aerosol-producing equipment but makes no mention of aerosol-producing procedures. It is also noteworthy that most of the equipment listed except for centrifuges is seldom used in recombinant DNA research. The most prevalent manipulations in laboratories using recombinant DNA technology with microorganisms are the growth of cul-

tures which is usually by shaking and/or aeration and the processing of these cultures by centrifugation. It is also well known that substantial aerosols can arise by aeration of cultures during growth and similarly in the filling of centrifuge tubes, in the removal of supernatant fluids and in the suspension of sedimented cells. This is particularly true when using cultures and/or suspensions of one liter or more. Thus, even if centrifugation is done in sealed rotors or using safety centrifuge cups, it is still important to load and unload centrifuge rotors using a biological safety cabinet. There are also water baths and other means to preclude distribution of aerosols arising from aerated growth of microorganisms containing recombinant DNA. These issues should be clarified since some laboratories around the country operating under P2 containment do not have biological safety hoods and others do. Certainly if such hoods are not necessary, it will be a substantial saving of equipment monies that could be used for other purposes.

10. Section II-D. Biological Containment (p.33075). I noticed a few grammatical or typographical errors in this section (organelle DNA rather than organelle vector, O replaced by λ and conjugative plasmid rather than conjugation-proficient plasmid) but a few more substantial problems are enumerated below.

11. Section II-D-1. Levels of Biological Containment (p.33075). In this section, it states "Any combination of vector and host which are to provide biological containment must be constructed" (my underlining) which seems at variance with the statement in the Decision of the Director to Issue Revised Guidelines that wild-type organisms might be allowed as components of HV1 systems. The above wording would certainly seem to preclude the use of wild-type host-vector systems as would the requirement in Section II-D-2-b-(1) dealing with approval of HV1 systems wherein it states that an investigator must submit "data on any mutations which render this organism less able to survive or transmit genetic information". The intent of NIH should, therefore, be clarified. In resolving this issue, it should be noted that even prototrophic "wild-type" *E. coli* K-12 strains are not equivalent to wild-type *E. coli* strains recently isolated from nature since the K-12 strain has acquired mutations during its long maintenance under laboratory conditions causing LPS and K antigen syntheses to be defective. These laboratory-acquired mutations certainly contribute to biological containment. Thus in deciding on requirements for HV1 systems, one should not discount the importance of laboratory-acquired as opposed to induced mutations and should use the term "wild-type" in reference to the usual phenotype associated with strains of the species recently isolated from nature.

12. Section II-D-1-a-(1) EK1 (p.33075). Most host components of EK1 systems used in recombinant DNA research have mutations in addition to those acquired during K-12's laboratory sojourn that confer nutritional requirements, cause recombination to be defective, etc. and thus are not wild-type prototrophic strains of *E. coli* K-12. Indeed, it is known that certain of these mutations very much diminish survival in the intestinal tract or in other environments and/or reduce the likelihood for transmission of recombinant DNA. While the inclusion of such mutations in any newly developed host strains to be employed as components of EK1 systems should not be mandatory, it might be wise to encourage it. I make this suggestion because, during the International Congress of Microbiology Meeting in Munich this past week,

I learned that 4 of 24 human volunteers who had been fed strains of E. coli K-12 in a risk assessment experiment being conducted in Great Britain excreted low titers of the E. coli K-12 strain for periods of up to four weeks. These results as well as those obtained by Rolf Freter (J. Inf. Dis. Vol. 137:624, 1978) in which prototrophic K-12 strains were found to persist in some animals under some conditions implies that the use of K-12 hosts without mutations to diminish their survival and/or ability to transmit DNA cloned on nonconjugative plasmid vectors will result in a higher cumulative amount of transfer of such recombinant plasmids to other microorganisms in nature than would occur if the K-12 hosts possessed mutations to diminish their survival and/or transmission ability.

13. Section II-D-1-c-(2) (p.33075). The requirement that "Reversion to host-independence must be less than $1/10^8$ per vector genome per generation." is operationally difficult, if not impossible, to define since there is no meaningful operational definition of the term generation when applied to plasmids or to bacterial viruses. Quite possibly this should be clarified and put into some terminology of frequency starting from single plaques or cells containing plasmids.

14. Section II-D-2-a. Responsibility (p.33075). The statement that "HV1 systems other than E. coli K-12 and HV2 and HV3 host-vector systems may not be used unless they have been certified by the NIH", in view of the lists not contained in Appendix A, effectively precludes already approved recombinant DNA research with the B. subtilis and Saccharomyes cerevisiae cloning systems except for self cloning. It thus becomes important that NIH through the RAC begin to develop procedural means to inform the scientific community of exactly how to get approval of HV1 systems and to begin to develop appropriate guidelines for the performance of experiments that are permitted under the Current Guidelines but which will not be initially permitted under the Revised Guidelines.

15. Section III. Containment Guidelines for Covered Experiments (p.33076-33084). For the most part, I think that containment specifications are adequately justified by the available data on the increased safety of using E. coli K-12 host-vector systems but I do have a few minor points to make and one major reservation as detailed below. I should note that the statement on page 33058 (Col. 1) enumerating the criteria used to classify experiments is extremely good. One point which was omitted from the list concerns the potential consequences of transfer of the vector containing recombinant DNA to some other natural host or vector.

16. Section III-A-2-a. Viruses of Eukaryotes (p.33077-33080). There are numerous instances in which the stipulated containment is P3 + EK1 or P2 + an EK1 host and a vector certified for use in an EK2 system. The specified use of a vector certified for use in an EK2 system in the absence of its certified host is inconsistent with other sections of the Revised Guidelines which consider hosts and vectors as inseparable components of EK1 and EK2 systems. More importantly, this allowance permits wide differences in the actual level of biological containment dependent upon the selection of the vector that has been certified as a component of an EK2 system. All bacteriophage lambda vectors certified as components of EK2 systems possess mutations which cause their replication to be dependent on the propagating host, block lysogenization and cause death of all host cells infected. Indeed, the lambda vector constructed by Donoghue and Sharp meets EK2 standards irrespective

of the propagating host. Although the lambda vectors constructed by the Blattner and Leder groups require use of either the DP50 or DP50 supF host, it is evident from the data provided by those laboratories and now substantiated by other investigators that the lambda vectors alone come very close to satisfying the level of containment required for EK2 certification all by themselves. Thus the use of a lambda vector that has been certified as a part of an EK2 host-vector system provides biological containment that would be equivalent to EK1.8 to EK2. On the contrary, with EK2 plasmid-host systems, almost all biological containment is provided by the host and little, if any, by the plasmid vectors which do not have mutations causing them to be dependent on the host. The plasmid vectors pMB9, pBR322 and pBR313 have defects which cause them to be mobilization-defective (Mob^-) but this only decreases their probability for transmission 1000 to 10,000 fold when compared with the mobilization of unmodified Mob^+ ColE1-derived vectors. It should be noted that the Mob^- defects of pMB9, pBR313 and pBR322 can be complemented by the ColK plasmid (Dougan et al, J. Inf. Dis. Vol. 137:676, 1978). It is also known that the low frequency of transmission of these plasmid vectors from χ1776 is also due to the conjugation defectiveness of χ1776, to the fact that χ1776 rapidly dies under nonpermissive conditions leading to its inability to transmit plasmid vectors and to the presence of a mutation causing a requirement for thymine or thymidine which leads to a marked reduction in the probability of transmission of plasmid vectors under nonpermissive conditions. These nonconjugative plasmid cloning vectors can also be transmitted from one microorganism to another by generalized transduction and this is diminished substantially in χ1776 which is partially or totally resistant to the generalized transducing phages P1, D108, Mu, etc. and which possesses a thyA mutation that reduces transductional transmission of plasmid vectors under nonpermissive conditions. I should indicate that James Robeson in our laboratory has shown that the generalized transducing phage, P1, can infect 70% of over 500 wild-type strains of E. coli tested and there is a substantial amount of literature to indicate that P1 has a very broad host range and is able to infect strains of Salmonella, Shigella, Klebsiella, etc. These results suggest that transductional transmission of nonconjugative plasmid vectors (which are not dependent on their propagating host) may contribute to plasmid transmission. It is therefore evident that the use of plasmid vectors that have been certified as components of EK2 plasmid-host systems provide only nominal biological containment compared to the use of lambda vectors which have been certified as components of EK2 phage-host systems. I should also point out that the reference to these plasmid vectors that have been certified as components of EK2 host-vector systems as "non-mobilizable" in Appendix F to the Proposed Environmental Impact Statement (p.33168) is erroneous. It is thus evident that experiments classified in Section III-A-2-a as requiring either P3 + EK1 or P2 + an EK1 host and a vector certified for use in an EK2 system can actually be done under P2 + EK1.1 if the investigator chooses to use a plasmid vector certified as a component of an EK2 host-vector system. Furthermore, the actual level of biological containment might even be less if the investigator selected an E. coli K-12 host like some of those used in the feeding experiments mentioned above.

Although the consequences of transmission of vectors containing viral DNA to other microorganisms is not discussed in Appendix E or F to the Proposed Environmental Impact Statement (p.33159-33169), Dr. Wallace Rowe has informed me that some consideration was given to this issue. Although I concur that working with viral DNA

inserts in E. coli K-12 is probably safer than working with the intact infectious virus, I do have reservations based on the lack of appreciation by the various groups that studied and reviewed the cloning of viral DNA in E. coli of the differences between phage and nonconjugative plasmid vectors and the consequences of transmission of recombinant DNA to wild-type microorganisms in nature. The recent results of experiments with polyoma in E. coli K-12, conducted by Dr. Michael Fried in Great Britain and by Drs. Malcolm Martin, Wallace Rowe and their colleagues in the U.S., also contribute to my concern. As you will recall at the Falmouth Workshop, while it was the consensus that one could not likely convert E. coli K-12 into a pathogen, much less an epidemic pathogen, there was considerable concern and debate about the consequences of transmission of vectors containing recombinant DNA to microorganisms indigenous to various natural habitats. I am also informed that certain virally specified mRNAs need not be processed to lead to synthesis of fully functional viral proteins and that some virally-specified proteins can be made using E. coli RNA polymerase with an E. coli generated translation system. I thus believe that this section of the Revised Guidelines dealing with the cloning of viral DNA in E. coli K-12 host-vectors needs to be examined not only by virologists but by some of the types of experts who were in attendance at the Falmouth Workshop Meeting.

In view of what I have read and learned and based on some of the preceding comments, I would not have voted in favor of lowering the containment levels for cloning viral genetic information in E. coli K-12 to the levels now stipulated in the Revised Guidelines if I were still a member of the RAC. This is particularly true in view of the fact that the risk assessment experiments which were to have defined what levels of containment are fitting have yet to be completed.

17. Section III-B-2. Return of DNA segments to non-HV1 host of origin. (p.33080). The provisions of containment for a prokaryote which does not exchange genetic information with E. coli, the so-called Host B, are poorly thought out and in need of refinement. For example, if Host B is a Class 1 agent, the cloning into E. coli would require P2 + EK1 or P1 + EK2 and the return of the potential double vector to Host B would only require P1 containment. If Host B were a Class 2 agent, and this is not precluded, then the nonsymmetry of the containment required and the problems associated with double vectors become even more exaggerated. Obviously, these points need to be addressed and further refinement of this section is needed. Based on comments in the Decision of the Director to Issue Revised Guidelines statement, I surmise that it was intended to use the cloning in E. coli K-12 to purify a genomic segment from Host B which would then be separated from the E. coli vector, purified and returned to Host B in the absence of the E. coli vector. I should add that it might be wise to note in this section that P2 containment would be advisable if Host B is a Class 2 agent or a plant pathogen.

18. Section III-C-5. Fungal or Similar Lower Eukaryotic Host-Vector Systems (p.33084). The stipulations for cloning DNA from a non-HV1 host into E. coli K-12 and return to that host (designated Host C) result in the same problems detailed in the immediately preceding comment.

19. Section IV. Roles and Responsibilities (p.33084-33087). I believe this section has been thoroughly thought out and clearly written. I wholeheartedly support the concept that an institution receiving NIH funds should be responsible for adherence to the Guidelines even when recombinant DNA research at that institution is not necessarily supported by NIH funds. I also believe that greater reliance needs to be placed on the Institutional Biosafety Committee and the proposals contained in Section IV will both better facilitate the research and result in better adherence to the Guidelines because of greater local responsibility. I also think that the insistence on a biological safety officer for institutions conducting P3 and P4 level research is a wise decision which I fully support.

20. Section V. Footnotes and References (p.33087-33089). Most comments I had pertaining to this section have been given above. I should note in reference to footnote 1 and Appendix B to the Proposed Revised Guidelines (p.33089-33090) that the current listing of etiologic agents is incomplete and in some respects inaccurate. For example, under fungal agents that are Class 2 agents, one finds Actinomycetes which first of all are bacteria, not fungi. Furthermore, the term "Actinomycetes" is a group designation which includes among its eight families the genera Actinomyces, Nocardia, Streptomyces and Mycobacterium and all of these are then classified as Class 2 agents. Since most species of Streptomyces and many of Nocardia and Mycobacterium are harmless soil bacteria, I hope the revision of the list of etiologic agents will rectify these problems and errors. I might also note that Rickettsia and Chlamydia are obligate intracellular bacterial parasites and not viral agents and should thus be classified under the bacteria.

21. In view of my comments concerning biological containment of the E. coli K-12 host-vector systems and the large difference between the containment, and in some instances utility, provided by EK1 vs EK2 systems, it might be worthwhile for NIH to reconsider Dr. Waclaw Szybalski's suggestion of several years ago to specify EK1.5 systems. In this regard, we have a reasonable number of well characterized strains already in our collection that should, in conjunction with nonconjugative plasmid vectors, satisfy anticipated requirements for such an EK1.5 level of biological containment.

Although my comments have been numerous and lengthy, I wish to reiterate my enthusiastic support for adoption of the Proposed Revised Guidelines for Recombinant DNA Research following refinement and/or reconsideration based on comments I and others have made. If I can provide any additional information or advice, I would be pleased to do so.

Sincerely yours,

Roy Curtiss III

RCIII/pp
Enclosures

the University of Alabama in Birmingham / UNIVERSITY STATION / BIRMINGHAM, ALABAMA 35294

the Medical Center / DEPARTMENT OF MICROBIOLOGY / July 18, 1978

Dr. John Spizizen
Department of Cellular Biology
Scripps Clinic and Research Foundation
La Jolla, California 92037

and

Dr. Donald Helinski
Department of Biology
University of California, San Diego
La Jolla, California 92093

Dear John and Don:

I am writing in response to your letter of July 10th concerning Appendix A to the Guidelines for Recombinant DNA Research. The proposed Appendix A to the NIH Guidelines as presently written is not acceptable to me. One can adopt either a liberal or a conservative position in deciding what organisms to list and in what groupings but with either approach, one must be consistent. I find fault with the proposed Appendix A since it is not consistent and it is also incomplete. Such inconsistency and incompleteness will raise havoc in the scientific community and utter confusion on the part of those charged with interpreting the Guidelines and enforcing the regulations associated therewith.

In order to illustrate the various perspectives one can take on Appendix A, I will enumerate some principles (conservative or liberal) and give some examples. I should indicate at the outset that I am not recommending one or the other approach but rather that one should be consistent and in doing so one can amass appropriate literature citations to support the particular stance taken.

The Conservative Position

In Appendix A, include groupings of those species in which stable inheritance of expressed chromosomal genes by genetic recombination and/or by gene pickup on a plasmid has been demonstrated.

Examples

List 1. *Pseudomonas aeruginosa* into *Escherichia coli*. This type of transfer with stable inheritance of expressed chromosomal genes has been demonstrated to occur and thus justifies the cloning of any and all DNA from *Psuedomonas aeruginosa* strains into *Escherichia coli* strains. The reciprocal cloning of *E. coli* DNA into strains of *Pseudomonas aeruginosa* would not be permitted if one

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adopts an ultra conservative point of view. Espousing the ultra conservative point of view, one could hold that E. coli chromosomal genes might not be expressed in P. aeruginosa and thus cloning of E. coli DNA into various strains of P. aeruginosa should not be permitted outside the Guidelines until such had been demonstrated by experimental data. On the other hand, with a somewhat liberal point of view one can argue that the reciprocal could also occur naturally.

List 2. Citrobacter freundii into Escherichia coli. The same considerations as enumerated above can be cited.

However, in the absence of data, one could not clone Citrobacter freundii DNA into Pseudomonas aeruginosa or vice versa outside of the Guidelines even though both C. freundii and P. aeruginosa can exchange with E. coli.

Thus based on a conservative approach, one would have a variety of groupings depending upon published data with the possibility that one could permit reciprocal cloning even though the data were only unidirectional from one donor to one recipient, a somewhat more liberal stance.

A second factor to consider in the conservatice approach deals with how much credence one wishes to place on taxonomic relationships using whatever taxonomy (i.e., Bergy's Manual) one chooses. In this regard, Escherichia coli as one species has almost as much diversity as the entire genus Salmonella and the genus Pseudomonas has as much or more diversity than all the species in the family Enterobacteriaceae. Thus to include all Pseudomonas species on one list in the absence of data is contrary to the conservative approach. In other words, there is data to show that P. aeruginosa, P. putida, P. glycinea and a few other species do indeed have the capability of transmitting plasmids and/or chromosomal DNA to E. coli K-12 but such data is not available for the vast majority of Pseudomonas species. Thus using a conservative approach, one could not list all species of Pseudomonas or for that matter all species of any of the genera listed in the present Appendix A since the data does not exist in the literature.

The Liberal Position

Include all those species and/or genera if any type of gene transfer occurs (transformation, transduction and/or conjugation including plasmid transfer). In this case, the data which show that broad host-range plasmids can pick up chromosomal DNA from one species and transfer and have it expressed in another, even though guanine-cytosine contents of the DNA are highly divergent, could be used to argue that the existence of any transfer mechanism would allow for the formation of any and all recombinant types by natural means. Thus using the liberal philosophy one would include essentially all gram negative microorganisms and allow cloning from one to another in all reciprocal arrays.

Consistency Issues

Independent of whether one adopts either the conservative or liberal position in arriving at groupings of organisms where cloning would be outside the Guidelines, one should be consistent in using genus and species names or only genus names. The present list in Appendix A is inconsistent. Thus it would appear that all species of Pseudomonas are included based on data from studies with only several species whereas in the genus Agrobacterium which only contains 4 or 5 species only cloning with A. tumefaciens is excluded.

If the basis for the groupings in Appendix A is data on genetic exchange, then the pathogencity and/or virulence should not be a factor. It now appears that the vast majority of plant pathogens which are species of Pseudomonas and Erwinia can be used in cloning experiments outside the Guidelines (and even when data to verify that exchange does occur is generally lacking) whereas cloning with species of Vibrio, Pasteurella and Yersinia will still be under the Guidelines (even though data are available to demonstrate exchange - at least with E. coli). I should also point out that the economic costs in the U. S. associated with diseases caused by Erwinia and Pseudomonas species are far in excess of those associated with diseases caused by Vibrio, Pasteurella and Yersinia species. If pathogenicity is to be an issue, I suggest that NIH consult some expert plant pathologists, as well as veterinarians and infectious diseases experts.

Other Points

In terms of other points for your consideration, I think it should be clear (and maybe it is elsewhere in the Guidelines) that one could use recombinant technology for cloning DNA from an organism into itself as though it were equivalent to any other genetic tool of analysis. In this regard, it should be possible to use recombinant technology to study the genetics of a class 3 etiologic agent using derivatives of that same class 3 etiologic agent.

There should be a list of Bacillus species that can be cloned one into another, etc. outside of the Guidelines and similarly a list of Streptococcus species that exchange chromosomal DNA. I might add in terms of Streptococcus that although S. mutans chromosomal DNA can be transformed into S. sanguis, that S. mutans subspecies have DNA going from 34 to 46% guanine + cytosine. I surmise that other absurdities are also perpetrated by Bergy's Manual.

You have an unenviable task and I commiserate with you. Nevertheless, I implore that you be consistent. In this instance trying to be a middle roader will result in nothing but chaos. I will be present at the Advisory Committee Meeting at the beginning of August and so will be pleased to discuss this matters with you at that time.

Sincerely yours,

For Roy Curtiss III

Roy Curtiss III

RCIII/pp

Appendix C

Guanine-Cytosine Contents in Bacterial DNA*

Genus	Range of G-C Contents (percent)
Escherichia species	50-52
Citrobacter species	52-53
Salmonella species	50-54
Shigella species	50-52
Klebsiella species	53-60
Enterobacter species	55-58
Serratia species	53-60
Erwinia species	50-57
Pseudomonas species	48-69
Rhizobium species	58-65
Acinetobacter calcoaceticus	42-43
Agrobacterium tumefaciens	59-62
Rhodopseudomonas sphaeroides	∿71

* The guanine-cytosine contents are taken from Handbook of Microbiology (Vol. II, p.585-691) and the ranges for species within each genus are based on those species designated as belonging to that genus in Bergey's Manual of Determinative Bacteriology (8th edition).

The University of Iowa
Iowa City, Iowa 52242

College of Medicine
Department of Biochemistry

1847

September 23, 1978

Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Sir:

I would like to make the following comments concerning the proposed revision of the NIH Guidlines for Recombinant DNA Research:

1. Because E. coli K12 does not proliferate outside of lab environments, I feel that the general lowering of restrictions should be carried out at least as far as proposed. Also, I am in favor (for the reasons cited in your discussion of the proposed revision) of the following points:

2. Mouth pipetting should not be prohibited under P2 conditions and should definately be allowed under P1 containment. Mechanical pipetting devices may be improving but nothing comes close to the efficiency of mouth pipetting.

3. Eating and drinking should still only be prohibited in the work area under P2 conditions. Some labs have office desks in the lab (although separated from the lab benches) where researchers keep books, files, and perform paperwork. One should be allowed to have a cup of coffee or grab a sandwich while reading, for example.

4. In view of the safety of E. coli K12, P2-EK2 experiments should have a P3-EK1 option.

Sincerely,

Bruce Citron

Bruce Citron

[A-323]

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Executive Director

September 24, 1978

Dr. Donald Fredrickson
Director
National Institutes of Health
Bethesda, Md. 20014

Dear Dr. Fredrickson:

Enclosed herewith is the balance of comments referred to in my letter to you of September 22, 1978. Our complete set of comments on the proposed revised Guidelines is comprised of three sections:

Structures and Procedures

Technical Analysis and Comments

Protection of Employees

We look forward to the inclusion in the Guidelines of the many suggested changes offered by our own organization and others groups and individuals on behalf of the public health interest.

With all good wishes for a fruitful and speedy deliberation,

Yours very truly,

Francine Robinson Simring

Francine Robinson Simring
Executive Director

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TECHNICAL ANALYSIS AND COMMENTS

ON PROPOSED REVISED GUIDELINES FOR RECOMBINANT DNA RESEARCH

FEDERAL REGISTER, JULY 28, 1978
PART IV

INTRODUCTION

This section of comments on proposed revisions concerning the technical aspects of recombinant DNA experimentation is the second of a three-part report submitted by the Coalition for Responsible Genetic Research.

Part I - Structures and Procedures
Part II- Technical Analysis and Comments
Part III-Protection of Employees

A. "Exchangers"

The proposed revised guidelines contain a list of prokaryotes which are purported to be "exchangers"; i.e. they can either be shown to exchange chromosomal DNA in the laboratory, or their DNA homology is 20% or greater (pp. 33089, 33158). Recombinant DNA from any organism on the list would be permitted to be propagated in any other organism on the list. This kind of work would be exempt from the Guidelines.

1. Most of the organisms are listed by genus, when the available evidence only addresses possible exchanges between particular species of any of the genera. The extent of interspecies exchange within the genus Pseudomonas has not even been well-characterized. Only organisms designated by species can

legitimately be considered part of an "exchangers" list, and then only where more detailed information is available (see below).

2. Natural rates of exchange have not been taken into account in arriving at the list of "exchangers". The demonstration of any degree of chromosomal DNA exchange is sufficient for membership on the list. Thus, while only prokaryotes are on the present list, the consistent application of this principle could ultimately place eukaryotes and prokaryotes on the same "exchangers" list (that is, exempt from the Guidelines) since some limited exchange has undoubtedly occurred between certain pairs (i.e. Agrobacterium tumefaciens and its host plant).

3. The rationale for membership on the "exchangers" list completely ignores ecological considerations. For example, recombination experiments between wild type strains of E. coli (those strains which inhabit the normal human large intestine) and Salmonella (some species of which are responsible for severe food poisoning) are proposed to be exempt from the Guidelines, presumably because some species of these genera can exchange chromosomal DNA in the laboratory. There is no discussion of whether these microorganisms ever occupy the same ecological niche, and thus have the opportunity to exchange in nature. Fredrickson, in his statement, talks about the lack of success in converting E. coli K12 into a pathogen by insertion of Salmonella genes (p. 33059). Has this been attempted with wild type E. coli? Under the proposed revised Guidelines, such an experiment, with a host with none of the inherent weaknesses of K12, could be performed subject to no regulations.

RECOMMENDATIONS: Members of the "exchangers" list should be designated only by species name, and only where exchange can be demonstrated in a realistic ecological setting at a non-vanishing rate. Furthermore, recombination between members of the list should be subject to P2 physical containment and thus remain within the Guidelines.

B. *Cloning of Animal Cell Transforming Viruses*

The proposed revised Guidelines accept the recommendations of the "Ascot Conference" and have lowered containment levels for the cloning of animal cell transforming viruses (such as polyoma and SV 40)(p.33077). This decision does not take into account the results of the Rowe-Martin risk assessment experiment with polyoma, preliminary results of which were reported at the 1977 Falmouth Conference, but were not included in the published proceedings of the conference (Journal of Infectious Diseases, April 1978).

The most recent summary of these experiments were reported by Wallace Rowe at the Recombinant DNA Advisory Committee meeting of August 1-3, 1978. Briefly, it has been shown that polyoma DNA itself, de-proteinized, without a capsid(virus coat) can cause infection when injected into the bloodstream or or fed into the colon of a mouse. Roy Curtiss, in a letter to Fredrickson dated April 12, 1977 stated that he believed that such experiments would not give positive results. This unexpected result of the risk assessment experiment has received no publicity apart from informal statements by the investigators.

The significance of the experiment lies in its demonstration that polyoma DNA itself is an etiologic agent. Incorporated into a plasmid it is not infective, but if the plasmid is cleaved by a nuclease (which are ubiquitous) it is rendered infective. Thus one of the scenarios envisaged by critics of recombinant DNA research, i.e. that a disease-causing agent might be carried to new ecological niches by such experimentation, is now close to realization. All that is required for such a result is the lowering of physical and biological containment for these experiments. Polyoma DNA in a capsid can thrive only in intra-cellular environments; polyoma DNA in bacteria can thrive (and be

infective) in intestines.

RECOMMENDATION: Experiments involving mammalian transforming viruses should be performed at P4-EK2 containment levels.

C. *Shotgun Cloning of DNA* (p. 33077)

The proposed revised Guidelines distinguish between shotgun cloning of DNA from organisms which are known to produce potent polypeptide toxins and those which do not. Since many "normal" substances produced by any vertebrate (hormones, neuro-transmitters, cell recognition factors) would be highly toxic if presented at the wrong time or place to another animal, this distinction is meaningless.

RECOMMENDATION: All vertebrate shotgun experiments should be considered to involve producers of polypeptide toxins, and thus be performed under P3-EK2 containment.

D. *"Flexibility"*

The proposed revisions have a provision for "flexibility" that would allow, for example, experiments designated at the P3-EK1 level to be performed at the P2-EK2 level (pp. 33074, 33113). Since distinctions between the various P levels, up to P3, are very dependent in practice on training and diligence of personnel, it would seem that the validity of the trade-off would vary from laboratory to laboratory. Up to P3 it would seem that biological containment would be most reliable, but trade-offs in certain cases would probably be reasonable.

However, P4 represents the closest situation we have to absolute containment. For experiments designated at this level to be done at P3 containment would represent a serious falling away from the most stringent conditions which have been reserved for those experiments generally acknowledged to be in the highest risk category.

RECOMMENDATION: No other physical containment level should be substituted for the P4 designation without in-depth study by the RAC and the NIH Director of the specific experiment proposed.

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COMMENTS ON PROPOSED REVISED GUIDELINES FOR

RECOMBINANT DNA RESEARCH
FEDERAL REGISTER, JULY 28, 1978
PART IV

INTRODUCTION

This section of comments on the proposed revised Guidelines concerning protection of the health of the potentially exposed worker is the third of a three-part report submitted by the Coalition for Responsible Genetic Research.

Part I - Structures and Procedures
Part II - Technical Analysis and Comments
Part III- Protection of Employees

The following comments indicate areas of inadequacy, recommend improvements and changes, and also touch on the mechanism for policy change:

I. *Industrial Regulation*

The Guidelines provide only for voluntary compliance by industry with its standards and procedures. "...provision is now made for the private sector to register voluntarily its recombinant DNA activities with the NIH." (p. 33045) Because of the voluntary nature of the directive, industry will not be subject to sanctions for non-compliance. This is especially of concern because volume-oriented production sharply increases the probabilities of biologic mishap and worker exposure.

II. *Environmental Monitoring*

The proposed revised Guidelines provide no stipulations for environmental monitoring for recombinant DNA materials. Indeed, a mechanism for monitoring for presence in the air does not yet exist for much of recombinant DNA material.

III. *Biological Monitoring and Medical Surveillance*

The Guidelines are inadequate in their specifications for biologic monitoring and medical surveillance. The institution would be given responsibility for the determination "in connection with each project, the necessity for medical surveillance of recombinant DNA research personnel..." (p. 33084 IV-A-1-e). Such a program "might include, for example, records of agents handled, active investigation of relevant illnesses acquired by recombinant DNA research personnel and the maintenance of serial serum samples". Such wording offers the institution the option of determining that there is no need for medical surveillance.

The lack of specificity of the Guidelines' language in this area of protection of employees may well exclude some worker populations. Stipulations for "research personnel" does not provide for members of the custodial, maintenance and janitorial groups. Often these latter groups are at special risk because of their lack of knowledge of their conditions of exposure. Further, if each institution is given responsibility for each project under its aegis, the variability in program development and implementation among diverse institutions would provide for the exposed worker unequal protection under the law.

IV. *Worker Education*

Guideline requirements for educating workers about the potential hazards of working with recombinant DNA materials are inadequate and vague. While it is stated that the NIH has a contract with the American Society for Microbiology

to develop "minimum standards for training participants in recombinant DNA research " (p. 33053), once again other worker populations such as custodial, maintenance, and janitorial employees are overlooked. This lack of attention to the needs of non-research personnel for education is also illustrated in the directive to the principal investigator who shall "make available to the laboratory staff copies of the approved protocols that describe the potential biohazards and the precautions to be taken." (p. 33085 IV-A-4-m-[1]) ~~Further~~,

The vagueness of some terminology can lead to ineffectiveness of collected data. For example, experience with industrial Material Safety Data Sheets, which in theory indicate the biohazards of exposure, reveals that it is necessary to require that these "protocols" specify both acute and chronic effects; not only those known with certainty but also those strongly suspected.

V. *Emergency Spills*

The Guidelines do not adequately treat the courses of action in the event of emergency spills. It is mandated that the Biological Safety Officer shall develop "emergency plans for dealing with accidental spills and personnel contamination..." (p.33085 IV-A-3-b). Also that the Institutional Biohazard Committee shall "review and approve emergency plans covering accidental spills..." (p. 33085 IV-A-2-d). Such directives permit utilization of varying levels of expertise among members of the IBC, et al. Only specific and detailed instructions in the Guidelines for emergency spills can overcome the problems of uneven expertise and institutional pressures.

VI. *Institutional Biohazard Committee*

The Guidelines omit representation of workers in their specifications for the constituency of the IBC. In addition, representation of experts trained in the fields of worker and public health is inadequate.

"The IBC shall be a committee...that has the experience and expertise to assess the safety of proposed recombinant DNA research projects...Its membership should include...disciplines relevant to recombinant DNA technology, biological safety and engineering. It is recommended that the IBC also include members knowledgeable about such matters as applicable law, standards of professional conduct and ractice, community attitudes, and the environment. It is recommended that at least one member be a non-doctoral person from a laboratory technical staff." (p. 33085 IV-A-2)

The use of the word "recommend" rather than "directed" or "mandated" or "required" permits the IBC's free rein to constitute their roster as they may desire. Further, the need for experts in epidemiology, virology, public health, industrial hygiene, infectious disease, etc. is not addressed.

VII. *Sanctions and Compliance*

The language employed in the area of sanctions and compliance is too weak to ensure compliance. "All NIH-funded projects involving recombinant DNA technology must comply with the NIH guidelines. Non-compliance may result in suspension, limitation or termination of financial assistance for such projects and for other recombinant DNA research at the institution."

VIII. *Mechanism for Policy Change*

Changes in policy are vested in the Director of the NIH. Unchecked, extensive powers governing recombinant DNA research which come under his purview include:

- the power to revise and amend the Guidelines (p.33086 IV-B-1b)
- the power to certify new host-vector systems (p.33086 IV-B-1c)
- the power to permit exemptions from experimental prohibitions (p.33086 IV-B-1e)

A sharing of these powers would help to ensure broader perspectives in crucial decision-making for the technology.

RECOMMENDATIONS: The following changes and additions to the proposed revised Guidelines will increase protection of the health of the worker and the public.

I. *Industrial Regulation*

The NIH Guidelines should be extended to include industry on a mandated basis.

II. *Environmental Monitoring*

Existing mechanisms for environmental monitoring should be required, and programs to develop necessary mechanisms be instituted.

III. *Biological Monitoring and Medical Surveillance*

1. All laboratories conducting recombinant DNA research should be required to keep official OSHA health and safety log forms.

2. National standards for medical surveillance programs specific for each class of organisms and group of experiments should be developed and promulgated, in consultation with the Advisory Committee (to be reconstituted as described below).

3. Medical surveillance should be required for all workers potentially exposed to recombinant DNA material, and when appropriate, their families.

4. Ongoing epidemiologic and bio-statistical analysis of the morbidity data should be required as it is accumulated at this central registry. In this manner, trends can be detected early on.

IV. *Worker Education*

The guidelines should specify clearly the required components of training and of biohazard education. Further, they should delineateboth acute and chronic, known and suspected effects of exposure to the specific host-vector system involved. This educational program must be made available to all potentially exposed workers.

V. *Emergency Spills*

A set of national standards should be provided for in the Guidelines for the handling of emergency spills. These standards should be drawn up by the reconstituted Advisory Committee to the Director, NIH.

VI. *Institutional Biohazard Committee*

The Guidelines should mandate that the membership include at least two non-doctoral laboratory staff persons and at least two members from the custodial and janitorial sectors. Membership should also include at least one physician trained in(clinical and research)infectious diseases, at least one epidemiologist and at least one environmental scientist. None of these may be affiliated with the institution involved.

VII. *Sanctions and Compliance*

In reference to the stipulation "Non-compliance may result in suspension..." (p. 33087 IV-D-1a), the word "may" should be stricken from the sentence and the word "shall" be substituted. Fines appropriate to the nature of violations should be levied in addition to the cessation of funding. In addition to the foregoing, criminal penalties should be levied for certain willful violations of the Guidelines.

VIII. *Mechanism for Policy Change*

The Recombinant DNA Advisory Committee to the Director of NIH should be reconstituted by Guidelines mandate to include representatives from OSHA, EPA, appropriate labor unions, at least one physician trained in(clinical and research)infectious diseases, at least one epidemiologist, at least one environmental scientist, and at least one medical microbiologist.

Only after consultation with and approval by the reconstituted Recombinant DNA Advisory Committee may the Director use his powers to revise and amend the Guidelines; to certify new host-vector systems; and to permit exemptions from experimentation prohibitions.

HARVARD UNIVERSITY
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Sept. 24, 1978

re: Recombinant DNA Guidelines

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland, 20014

Dear Dr. Fredrickson:

Bert Ely sent me a paper to review,"Transfer of Drug Resistance Factors to the Dimorphic Bacterium Caulobacter crescentus". He asked that I send you a letter regarding Caulobacter and recombinant DNA, based on this paper.

Ely's use of transposons is an exciting new way of labeling genetic material that is transmitted between organisms. I have already started similar experiments in Rhizobium. His evidence that $ColE_1$ replicates in Caulobacter is also very encouraging.

I feel that Bert Ely has demonstrated genetic exchange between Caulobacter and E. coli. I would therefore urge you to include Caulobacter in the list of exempted organsims found in Appendix A as described in Section I-E-4 of the Revised Guidelines.

Sincerely,

Harry Meade

Harry Meade

Environmental Defense Fund

1525 18th Street, NW, Washington, D.C. 20036 • 202/833-1484

September 25, 1978

COMMENTS OF THE ENVIRONMENTAL DEFENSE FUND ON THE PROPOSED REVISED NATIONAL INSTITUTES OF HEALTH GUIDELINES FOR RECOMBINANT DNA RESEARCH (43 Federal Register 33041-33178)

Introduction

The Environmental Defense Fund (EDF) is a non-profit organization with over 46,000 members. EDF undertakes legislative, judicial and administrative actions to minimize human exposure to toxic chemicals. EDF has been deeply involved in the national debate on recombinant DNA. In 1976, EDF petitioned the Department of Health, Education and Welfare (DHEW) to use its authority under §361 of the Public Health Services Act to regulate recombinant DNA activities. EDF submitted comments on the current National Institutes of Health (NIH) recombinant DNA guidelines and has testified before Congress and the Advisory Committee to the Director of NIH on this issue. EDF also testified at the DHEW September 15, 1978 public hearing on these proposed revised guidelines.

Scope of the Guidelines

I-A. NIH should stop calling its proposed procedures for guaranteeing environmentally sound handling of recombinant DNA "Guidelines" and instead refer to them as regulations. The distinctions between guidelines and regulations are important. Regulations clearly have the binding force of law, are subject to the rules of the Administrative Procedure Act and convey to the regulated the seriousness of the issue. Continued use of the term "Guidelines" implies that the procedures are

only suggested and do not have to be followed rigorously. NIH has revealed its sensitivity to the language of the proposed "Guidelines" in its recommendation to change the name of the Institutional Biohazard Committees to Institutional Biosafety Committees. It should manifest this sensitivity again and term these proposed procedures regulations. (Hereafter, these comments will refer to the proposed "Guidelines" as PRG-NIH).

PRG-NIH should apply to all recombinant DNA research conducted at an institution that receives DHEW funds for any purpose. Clearly, recombinant DNA research poses the same risk no matter where the research is carried out. DHEW should therefore expand the coverage of PRG-NIH to the maximum extent legally possible.

I-C. Paragraph three of this section conveys the false sense that all recombinant DNA research, regardless of the physical and biological containment levels required, can proceed solely on the basis of local approval. This section should be rewritten to indicate that according to PRG-NIH, prior NIH approval is required for initiation of all recombinant DNA activities, except changes in ongoing projects below the P-4 level and single-step reductions in containment levels for experiments with purified DNA and characterized clones. (EDF's contention that all changes in ongoing experiments should be initiated only after NIH approval is discussed in the last section of these comments.) EDF finds it shocking that the General Applicability section of PRG-NIH could contradict the rest of PRG-NIH on so fundamental an issue.

All NIH funded projects, regardless of where they are carried out, should meet the requirements of PRG-NIH. Projects carried out in countries with more lenient requirements should still have to meet

all of the NIH requirements. The responsibility of the American government to insure the environmentally sound practice of the export of American science and technology has received much attention in a variety of different forums. The U.S. Consumer Product Safety Commission recently banned the export of U.S. made TRIS treated sleepwear. TRIS is a carcinogenic flame retardant, originally banned by the Commission only from children's sleepwear sold in America. The ability of U.S. companies to export drugs not approved for sale in the U.S. has been the focus of much argument during Congressional consideration of the drug reform act of 1978. In that forum EDF supported language which would have prevented export of non-approved drugs. FDA regulations require that foreign generated research submitted for marketing license approval must get informed consent from subjects(21 CFR 312.20). Finally, the White House is currently deliberating the extent to which the National Environmental Policy Act should apply to U.S. funded projects overseas.

I-D. In the document entitled "Decision of the Director, NIH (DD-NIH), much is made of the fact that the U.S. DNA regulations are stricter than those of most other countries. It appears as if this comparison is being used by the Director as support for relaxation of the existing NIH guidelines. If so, this is completely unjustified. Unfortunately, the U.S. has found itself leading the world in a large variety of environmental and public health oriented regulations. This fact attests not to the radical progressiveness of American regulatory agencies but to the failures of foreign regulatory agencies.

I-D-2. As presently written, this section does not include any criteria for identification of "potent" toxins. The use of ambiguous terms such as "potent" is proper in legislation but not in regulations.

NIH should establish a list of toxins, experiments with which are prohibited.

I-D-5. The language in this subpart does not pay sufficient attention to the rate of natural transfer of DNA. The crucial issue to be resolved is whether the proposed experiment presents a risk of compromising the use of an animal or human drug, regardless of whether the DNA transfer also occurs naturally. The burden of proof should be on the experimenter to demonstrate that the experiment will not compromise the use of a drug.

I-D-6. The use of the language "after appropriate notice and opportunity for public comment" does not adequately specify procedures for public notice and comment. These procedures must be described, in detail, in the "Guidelines". Failing this the public will have no assurance that the opportunity for public comment will be provided. If pressure for a quick decision is strong or NIH wishes to avoid public scrutiny, the guidelines enable it to make decisions in secret. In addition, valuable resources are likely to be wasted fighting out the mechanism of "appropriate opportunity for public comment," each time the opportunity is given.

Within 10 days of receipt of an application for an exception from a class of prohibited experiments, NIH should publish in the Federal Register notice of the receipt, details of where the material submitted in support of the exception can be obtained and the closing date of the public comment period. At a minimum, the comment period should be 45 calendar days. Final notice of agency action should also be published in the Federal Register. All material submitted to NIH should be available to the public.

DD-NIH (43 Fed. Reg. 33048) indicates that the rationale for allowing exceptions from the classes of prohibited experiments is to provide for experiments for which there are "compelling social or scientific reasons reasons, for example, risk assessment experiments." This is an appropriately rigorous standard for approving exceptions. Yet I-D does not require that the benefits of the experiment must be compelling before an exception will be approved. I-D merely states that weight will be given in the decision making process "both to scientific and social benefits and to potential risks." Clearly, the standard for excepting experiments differs between PRG-NIH and DD-NIH. Yet only the "Guidelines" will have the indisputable force of law. With the PRG-NIH language, many potentially hazardous experiments which provide the potential for only minimal benefit may be excepted. The language of I-D should be changed to allow only experiments that will provide compelling benefits to be excepted.

This is only one example of where DD-NIH and PRG-NIH differ on extremely crucial issues. Yet again, only the "Guidelines" will have the indesputable force of law. DHEW should carefully screen the Environmental Impact Assessment, DD-NIH, and PRG-NIH to eliminate any contradictions. All information necessary for compliance should be written into the "Guidelines" themeselves and not remain scattered throughout the Federal Register package.

I-E-4. Recombinant DNA activities should be exempted from the "Guidelines" only if they do not present a significant risk to health or the environment. The criterion for granting exemptions should be safety and not whether DNA exchange already goes on in nature.

I-E-5. Once again, the public participation and public comment provisions of this section are too vague. New classes of recombinant DNA molecules should be exempted from the "Guidelines" only by regula-

tion. Proposals for exemptions should be published in the Federal Register along with notice of where background documents can be obtained. There should be a minimum 30-day public comment period.

Containment

II-A. This section admits that individuals engaged in recombinant DNA activities should receive "adequate instruction" in good microbiological practices. Yet PRG-NIH does not require that individuals complete specified training courses or demonstrate a certain level of competence. DD-NIH (43 Fed. Reg. 33053) indicates that while the Director feels that certification of adequate instruction is a good idea, NIH does not now intend to develop formal certification requirements. NIH concludes that because it currently has a contract with the American Society for Microbiology (ASM) to develop minimum standards for those engaged in recombinant DNA activities, formal certification requirements at this time are premature.

EDF disagrees with this conclusion. NIH should have targeted the ASM contract for completion in time for inclusion in PRG-NIH. Given its failure to do so, NIH should now take the steps necessary to issue formal certification requirements as soon as the ASM report is available. NIH should indicate in PRG-NIH that formal certification requirements will be issued as soon as the ASM report is complete. ASM should complete its contract at the earliest possible date. The responsibility for implementing the certification program should be given to the Institutional Biosafety Committee (IBC).

NIH also acknowledges that all recombinant DNA experiments with known or potential biohazards should have an emergency plan in case of accident. Yet PRG-NIH fails to require such a plan. NIH should

require that each recombinant DNA activity have an emergency plan. This plan should be approved by the IBC as part of the review process for each recombinant DNA activity.

II-D-2. The procedures for NIH certification of host-vector systems (HV) were generally agreed to be among the weaker procedural sections of the existing DNA "Guidelines". Indeed, the "Guideline" violation at the University of California of San Francisco was blamed on ambiguities in the NIH publications laying out procedures for HV certification. Unfortunately, PRG-NIH does not resolve these procedural ambiguities. II-D-2 needs to be rewritten.

PRG-NIH (43 Fed. Reg. 33076) states that certain new HV "may not be used unless they have been certified by NIH." PRG-NIH does not indicate which office within NIH supplies this certification. The person seeking certification does not know if he or she is free to use the HV after certification by the Recombinant DNA Advisory Committee (RAC) or if they must wait for approval by the NIH Director. An analysis of the Federal Register package does not clarify this issue.

PRG-NIH states (43 Fed. Reg. 33076), "When appropriate, the proposed host-vector system will be reviewed by the NIH Recombinant DNA Advisory Committee."

The Environmental Impact Statement states, (43 Fed. Reg. 33115), "Under the PRG-NIH, HV1 systems other than E. coli K-12 and HV2 and HV3 systems are considered by an expert working group and then by the RAC, which makes appropriate recommendations to the Director, NIH."

PRG-NIH also states (43 Fed. Reg. 33086), "Responsibilities of NIH. Office of the Director, NIH. The Office of the Director shall be responsible for: . . . . Certification of new host-vector systems."

Must all HV applications be approved by RAC? If only some do, then which ones? Whose certification is needed before use of an HV can begin? Can the Director go against the recommendation of RAC? These questions are left unanswered by PRG-NIH.

This section of PRG-NIH is another indication that the documents in the Federal Register package sometimes contradict each other. It also indicates that all information needed for compliance is not contained in PRG-NIH. For example, PRG-NIH do not describe the criteria for approval of EK2 HV. The reader of PRG-NIH would not know that such criteria exist. Yet DD-NIH (43 Fed. Reg. 33057) states, "It should be stressed that specific objective criteria do exist for approval of EK2 host-vector systems. These, however, do not appear in the Guidelines themselves, but rather as information in the Environmental Impact Assessment, Appendix H."

II-D-2 Completely silent on the issue of public notice and comment. This is completely unsatisfactory. Public notice and comment must be provided and specified in PRG-NIH. Section IV-B-1-e of PRG-NIH states that the Director shall certify new HV after "appropriate notice and opportunity for public comment." However, specific procedures must be written into II-D. Some discussion of this issue is contained in the DD-NIH (43 Fed. Reg. 33057): "I agree that prior notification to the public in the Federal Register should be given when the RAC considers applications for certification."

Notification of receipt of applications for certification of new HV should be published in the Federal Register within 10 days of receipt of the application. The Federal Register notice should specify where the material submitted in support of the application can be obtained by the public. The Federal Register notice should also specify

the closing date for public comment. The comment period should be no shorter than 45 days and should end in time for submissions to be circulated to whomever (RAC, ORDA, etc.) will be responsible for assessing the merits of the application. Notice of RAC meetings dealing with the application should also be published in the Federal Register and the meetings should be open to the public. Notice of NIH's final action should also be published in the Federal Register.

Roles and Responsibilities

IV-A-1-a. This section should specify a time by which the IBC must be established. EDF recommends that the IBC be established within 45 days of final promulgation of the PRG-NIH. The failure to specify a time limit for formation of the IBC is indicative of the overall failure of PRG-NIH to provide the specifity needed to guarantee compliance with the intent of the PRG-NIH. Without such a time limit, institutions are free to delay addition of needed public representatives for an unlimited time.

IV-A-1-d. Once again, this section fails to provide a time limit for IBCs to bring protocols into compliance with PRG-NIH. Without such a time limit, research not conforming to the safety requirements of PRG-NIH can continue for an unlimited amount of time. It is shocking that so elementary a regulatory concept is missing from PRG-NIH. (As described in our comments on I-C and Appendix C of PRG-NIH, EDF maintains that no recombinant DNA research at an institution receiving NIH funds for any purpose should continue unless NIH formally indicates that the containment requirements specified by the IBC are appropriate. Under this procedure the IBC would provide NIH with its assessment of the appropriate containment levels plus certification

that the laboratory in question can meet the requirements of those containment levels. Only upon receipt of NIH concurrence with the IBC assessment of the containment levels and laboratory competence, should the research project should be allowed to begin. This approach moots question of a time frame.)

However, if DHEW decides to allow certain experiments to begin after approval by the IBC, then a procedure for bringing protocols into compliance with the results of NIH review is a necessity. EDF suggests that NIH order the research to be halted until the protocols are brought into compliance. Another option would be to allow 15 days for protocol modification. If NIH did not recieve IBC notice of completed modification by this time, funds would be halted.

IV-A-1-e. PRG-NIH allows each IBC to determine whether a medical surveillance program will be instituted for a recombinant DNA activity. EDF recognizes the scientific difficulties inherent in monitoring the health effects of recombinant DNA research. However, in other regulatory arenas analytic methodology is often a prerequisite for use of a hazardous substance. FDA has proposed that analytic methodology for determining residues be a prerequisite for approval of carcinogenic animal feed additives (42 Fed. Reg. 10412). OSHA regulations require medical surveillance of workers contacting carcinogenic chemicals (see for example 42 Federal Register 54147). OSHA's experience has unfortunately revealed that without government intervention the voluntary establishment by regulated individuals of medical surveillance programs is extremely unlikely.

EDF recommends that NIH be required to determine the necessity for medical surveillance programs of recombinant DNA personnel. If

surveillance is ordered by NIH, then NIH should further specify the nature of the program required. If NIH determines that surveillance is not necessary, NIH should be required to present its reasons in writing to the IBC for the public record. This statement should be made available by the institution to those workers involved in the activity in question.

IV-A-2. PRG-NIH requirements for membership on IBCs do not insure that these committees will satisfactorily perform their oversight and regulatory roles. PRG-NIH essentially calls for peer review of recombinant DNA activities. Experience with Institutional Review Boards[1], medical licensing and disciplinary boards and the handling of violations of the existing recombinant DNA "Guidelines" by the biohazard committees of Harvard Medical School[2] and the University of California at San Francisco[3], demonstrate that peer review does not adequately protect the public. The collegial instincts of peer groups, the lack of regulatory and oversight experience of most academic personnel, and the desire of institutions to avoid negative publicity combine to make the performance of peer review groups completely unsatisfactory. PRG-NIH's attempt to solve this problem by

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[1] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Report and Recommendations Institutional Review Boards. U.S. Department of Health, Education and Welfare. DHEW publication No.(OS) 78-0009.

[2] Report of Ad Hoc Committee on Recombinant DNA at Harvard Medical School, April 18, 1978.

[3] Wade, Nicholas. Recombinant DNA: NIH rules broken in insulin gene project. Science 197: 1342-1345. September 30, 1977.

mandating that one IBC member cannot be affiliated with the institution completely fails to eliminate the problems of peer review. The PRG-NIH requirement clearly enables institutions to appoint zealous recombinant DNA researchers to IBCs, just as long as they work somewhere else. In addition, one non-affiliated member in a sea of paid university employees does not provide the balance and courage needed on an IBC.

EDF therefore maintains that the following membership ratios be mandated for all IBCs. One third of the membership of each IBC should be composed of individuals who have not been affiliated with the institution for at least one year prior to their service on the IBC. At least one of these individuals should be a non-doctoral person from a laboratory technical staff. This person should be elected by the institution's technical staff. At least one person should represent the health department of the local government. This person should be selected by the local health department. The remainder of the non-affiliated members should be persons who may be reasonably expected to represent the interests of the general public. DHEW's proposed regulations for the governing bodies of Health Systems Agencies also calls for persons who may be reasonably expected to represent the interests of the general public. (43 Fed. Reg. 22858)

IV-A-2-c. The failings of Institutional Review Boards, mandated by DHEW's regulations to protect human subjects of biomedical and behavioral research, and of the Harvard Medical School committee responsible for overseeing recombinant DNA research, indicates that specific NIH requirements for monitoring of ongoing experiments is essential. In the case of the Harvard committee (supra note 2), it is apparent that throughout the committee's long deliberations over the containment capabilities of Dr. Thomas' laboratory, no member of

the committee ascertained whether recombinant DNA experiments were being carried out. Here was a case where the committee was embarked on a detailed examination of a particular laboratory, subjecting it to far more scrutiny than usual for most laboratories, and yet the basic fact of whether research was being carried out was never determined. The experience of HEW with Institutional Review Boards (IRBs) is also illustrative. Many IRBs approve projects without any stipulation for subsequent review after the project is initiated. More than two thirds of the IRBs did not appoint someone to observe the manner in which projects were conducted. Twenty percent of the IRBs felt that research could be conducted in a manner substantially different from the approved protocols without the IRB being aware of the changes. Finally, there was little improvement between pre- and post-review versions of informed consent forms, despite IRB requests for modifications. (supra note 1) This illustrates a failure on the part of the IRB to follow through to insure implementation of its suggested modifications. A similar problem with oversight of ongoing experiments was revealed by Bradford Grey[1]. Grey concluded that many IRBs provided no continuing oversight of research projects. Moreover, several of the respondents in his study indicated that they would not conduct oversight because they thought it would inappropriately challenge a researcher's trustworthiness. (This reluctance to challenge the word of one's colleagues is another justification for EDF's suggestion that IBC's include members who can be reasonably expected to represent the general public.)

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[1] Human Subjects in Medical Research, John Wiley and Sons, New York, 1975.

In light of this experience, EDF suggests that, at the minimum, NIH require that an IBC inspect all laboratories carrying on recombinant DNA activities at least twice a year. This inspection should include review of physical containment equipment, the training of any new personnel hired, and laboratory notes to insure that no protocol changes were made that were unreported to the IBC.

Copies of these inspection reports should be available both through NIH and the IBC.

IV-A-2-f and IV-C-3. EDF maintains that all IBC meetings should be announced and be open to the public. All MUA's and project registrations should be publicly available. Public availability of these documents is crucial if the public is to oversee the performance of NIH and the IBCs. Without the information contained in these forms and presented at the IBC meetings, local community groups, individuals, local government agencies, etc., will be unable to determine if proper containment requirements are being followed for recombinant DNA experiments.

The DD-NIH states (43 Fed. Reg. 33065), "I do urge that local committees, when possible, have open meetings and suggest that all meetings be announced." However, this suggestion is not contained in PRG-NIH. Moreover, EDF disagrees with the DD-NIH statement (43 Fed. Reg. 33065) that IBC meetings cannot be open because of the possible discussion of proprietary and patentable information. This statement is based on an incorrect reading of applicable statutes and case law. EDF's reading of applicable statutes (5 U.S.C. §552 and 18 U.S.C. §1905) indicates that the information in IBC meetings, MUAs and project registrations, concerning the work of non-commercial scientists, must be released to the public by NIH.

The information in IBC meetings or project registrations of commercial scientists subject to the DNA guidelines should also be revealed to the public by NIH. 5 U.S.C. 552 allows NIH to disclose trade secrets. Moreover, EDF contends that the information EDF suggests should be released to the public, does not meet statutory or case law definitions of trade secrets or confidential commercial information. (5 U.S.C. §552(b)(4)); National Parks and Conservation Association v. Morton (498 F-2d 765 (1974)). Only protocols of experiments will be revealed to the public. Both the results and objectives of experiments will not be revealed. There is, therefore, no strong likelihood of substantial competitive harm resulting from release of this information. 18 U.S.C. §1905 provides a criminal penalty for violation of such an explicit prohibition against revealing trade secrets or confidential statistical information. However, no such prohibition here for information from commercial or non-commercial scientists exists. The courts have held that the research designs and protocols of non-commercial scientists are not trade secrets and, therefore, must be revealed to the public under the Freedom of Information Act. (Washington Research Project v. Department of Health, Education and Welfare, et. al., 504 F. 2d 238 (1974). This decision applies to all recombinant DNA activities whether or not the investigator plans to seek a patent on his research.

Because of the public policy advantages of releasing the information to the public and the clear legal authority of NIH to do so, EDF suggests that NIH establish a policy of making such information public. Any individual who feels wronged by such a policy has access to the courts for review of particular claims. The burden of proof should be placed by NIH on those individuals who wish to withhold

information from the public.

EDF also suggests that lay summaries of recombinent DNA activities be made available for each recombinant DNA activity.

IV-A-4-e. PRG-NIH should specify what types of protocol changes must be submitted to the IBC for approval. EDF will discuss this concern in more detail later in these comments.

IV-A-4-f. This section does not clearly indicate which recombinant DNA experiments may be initiated after IBC approval and which must await NIH approval. It seems to indicate that all activities can be initiated just on the basis of IBC approval. But other sections of PRG-NIH indicate that prior NIH approval is sometimes needed (see example Appendix C, section I-B and section D). In our comments on Appendix C of PRG-NIH, EDF maintains that no new recombinant DNA activity or change in existing protocols (e.g., change in the source of DNA or host-vector system used) should be initiated without NIH approval. If NIH chooses to disregard this suggestion, the agency must rewrite Appendix C, IV-A-4-f, I-C, and IV-A-2-a to clarify the procedural requirements that must be met before a new or altered recombinant DNA activity can be initiated.

This section should also specify a time limit for completion of changes mandated by ORDA (see section IV-A-1-d of these comments).

IV-A-4-m. The principal investigator should notify the IBC in writing of compliance with this section.

IV-A-4-n (3) and n(4). The principal investigator should halt any ongoing recombinant DNA activity if any work errors, work conditions, or problems in the operation of biological and physical containment practices result in a failure to meet assigned containment requirements of. The IBC should be notified within 24 hours of such

a situation. Failure to require cessation of work under these circumstances allows experiments not conforming to the regulations to continue. Cessation also provides strong incentive for quick correction of problem situations. A less satisfactory option would be to allow 10 days for repairs. Work would be halted if repairs were not completed by that time. The IBC should certify in writing that repairs have been made.

IV-B-1-b. PRG-NIH does not clearly describe procedures for future revisions of the "Guidelines". EDF maintains that the "Guidelines" should be revised by regulation, after public notice and comment. All proposed revisions should be published in the Federal Register, with a detailed preamble supporting the proposed changes. All relevant background information should be available to the public. A minimum 45 day public comment period should be provided. An informal public hearing should be held during the comment period.

IV-B-1-c. (See section II-D of these comments.) EDF agrees that no new host-vector system should be used in recombinant DNA experiments until it has been certified, via publication in the Federal Register, by the Director of NIH. However, this procedure must be clarified since section II-D of PRG-NIH does not clearly indicate which office in NIH must certify new host-vector systems. EDF's comments on section II-D provide our views on the nature of appropriate notice and public comment in this area.

IV-B-1-d. Section I-E of these comments contains EDF's views on the nature of appropriate public notice and comment for this area. EDF further maintains that a person applying for an exemption should be required to show that the activity in question does not present a significant risk to health or the environment. The mere fact that a

dangerous event also occurs naturally is not sufficient rationale for allowing its deliberate duplication in the laboratory, without safeguards. For example, we would never allow the dissemination of asbestos into the environment simply becuase it already occurs naturally.

IV-B-1-e. See section II-D of these comments for EDF's position on the nature of "appropriate notice and opportunity" for public comment.

IV=B-2. The role of the Recombinant DNA Advisory Committee (RAC) involves assessing the risks and benefits of proposed recombinant DNA experiments. Section III of PRG-NIH, is one large exercise in determining acceptable levels of risk posed by recombinant DNA experiments. The determination of acceptable risk levels is not a purely scientific function. Necessarily, such an exercise is value laden. No containment provisions are foolproof and the more effective the containment equipment, the higher the cost. The selection of an appropriate containment level for a particular experiment is, therefore, the result of weighing the potential harm caused by release into the environment of the biological material used in the experiment against the cost and inconvenience of containment measures.

It can reasonably be expected that persons of varying backgrounds and attitudes towards environmental protection, the value of basic knowledge, and the applied benefits of recombinant DNA experimentation will differ on the level of risk society should bear in order to allow particular experiments to go forward. In addition, both the risk and benefits of recombinant DNA experiments will be borne by the population at large, and not solely by those individuals in the research sciences. The researcher is often fond of relying on "the desire of the people for scientific discovery" to argue for increased funding and lowered

containment levels. Ironically, there is less enthusiasm for asking the same people to participate in those decision-making processes. Secretary Califano by convening the National Conference on Health Research Principles, recognizes that scientists and the public can differ on the proper directions for scientific research.

RAC is more than the typical advisory committee. It is a working group responsible for drafting proposed agency "Guidelines". The narrow experience of current RAC members is particularly visible in Section IV of PRG-NIH. RAC wrote this section yet RAC members have little experience in administrative law or regulation. (EDF is not familiar with Professor Redford's background.) PRG-NIH bears sad witness to this lack of expertise. Peter Barton Hutt, a member of the Advisory Committee to the Director of NIH and former General Counsel of the Food and Drug Administration, commented on PRG-RAC, "From an administrative law standpoint, the Guidelines are pedestrian and indeed, defective. The procedures embodied in the Guidelines simply do not reflect adequate attention to elemental concepts of law. <u>This is understandable, since they were developed by scientists rather than by experts in administrative law</u>."[1] (emphasis added)

EDF therefore recommends that the membership of RAC be reconstituted to include meaningful representation of individuals who represent the spectrum of the interests of the general public and who have demonstrated experience in regulatory affairs. PRG-NIH is completely silent on RAC membership. This is unacceptable.

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[1] Letter from Peter Barton Hutt to Donald S. Fredrickson, March 31, 1978.

EDF's current suggestions for RAC membership differ from those we suggested at the September 15 hearing. EDF proposes that at least one half of RAC consist of individuals who are not engaged in biomedical research and who can reasonably be expected to represent the interests of the general public. Of these individuals:

1. one should represent the Environmental Protection Agency
2. one should represent the Occupational Safety and Health Administration
3. one should represent the Food and Drug Administration
4. one should represent the Center for Disease Control
5. one should represent a state health department
6. the remainder should be individuals who can reasonably be expected to represent the interests of the general public. Of these at least one should represent the labor movement, and one should represent the public interest health and environmental community.

Currently, the only public members on RAC are two professors, one of law and the other of medical ethics. Clearly, these individuals cannot be said to represent the interests of the general public.

IV-B-2-a. A subcommittee of RAC, containing a majority of members who meet the criteria of reasonably representing the interests of the general public, should be the working group responsible for recommending all future modifications in section IV of the "Guidelines". This subcommittee will have the necessary experience in regulatory affairs to draft requirements that sufficently insure protection of health and the environment.

IV-B-2 and IV-B-2-f. A subcommittee of RAC, composed of a majority of members who meet the criteria of being reasonably expected to represent the interests of the general public, should be responsible for

recommending to the Director of NIH, exceptions from classes of prohibited experiments and exemptions from the "Guidelines". Such recommendations are clearly the result of more than scientific considerations. NIH acknowledges the public policy aspects of granting exceptions,"In making such recommendations, weight shall be given both to scientific and asocietal benefits." (43 Fed. Reg. 33086). The interpretation of the "significant risk" standard for allowing exemptions is also a public policy issue.

IV-B-3-a-(4). In order to minimize delays cause by paperwork, NIH should establish a time limit for ORDA analysis of requests for modifications in ongoing experiments and review of competing and non-competing recombinant DNA projects. EDF suggests that ORDA complete its independent assessment within 5 days of receipt of information from the IBC. There are currently 2 persons conducting such analyses for ORDA. EDF suggests that at least one additional person be added to ORDA staff in order to further reduce the time necessary to review information submitted by the IBC.

IV-B-3-a-(5). Section IV-A-2-f of these comments discusses EDF's contention that all registrations should be publicly available.

IV-b-3-a-(8). PRG-NIH should establish a time limit for ORDA review of IBC membership. EDF, in section IV-A-1-a, suggests that institutions be required to establish their IBC within 45 days after promulgation of PRG-NIH in the Federal Register. ORDA review of IBC membership should be completed within 75 days of PRG-NIH publication in the Federal Register. NIH should then allow institutions 15 days to bring IBCs into conformity with the "Guidelines". NIH funds for recombinant DNA research should be halted for any institution that fails to meet these deadlines. Firm time limits and sanctions are

necessary if institutions are to comply with the "Guidelines" in a timely fashion. Without such time frames, each case must be handled in an ad hoc fashion and the opportunity for delay is open ended.

IV-C-1. EDF's comments on procedures for regulating non-NIH funded projects will be discussed in the section of these comments dealing with Appendix C. It is EDF's contention that no recombinant DNA project at an institution, subject to the "Guidelines", should begin without NIH certification that the containment levels assigned by the IBC are appropriate.

IV-C-3-a. See section IV-A-2-f of these comments.

Appendix C

EDF maintains that no recombinant DNA experiment should be initiated or altered until NIH approves the IBC project approval.

II-E. EDF disagrees with the rationale for limiting NIH oversight only to changes in experiments which as a result of the requested change require P-4 containment. While EDF agrees that P-4 facilities should receive particular NIH attention, EDF is also concerned that if the IBC mistakenly assigns a P-4 experiment to another containment level, NIH will not be aware of this action until a MUA is forwarded to NIH. The potential for harm continues until NIH reviews the MUA. Therefore, at the very least NIH should require that all requested changes that result in a P-3 or P-4 classification be approved by NIH before work is begun. EDF is concerned that all changes in biological material used and the physical location of experiments requires the IBC to reassess the applicable containment requirements, laboratory design, and equipment. This reassessment, raises the possibility of IBC error. In addition, the pressure to approve a request for a change

will be great because of the ongoing nature of the project.

EDF therefore maintains that no change in an ongoing project should be initiated with NIH approval. The error rate of IBC's has been variously estimated at 4-15% by NIH's Office of Recombinant DNA Activities (ORDA).[1] Therefore, the potential for experiments to proceed without adequate safeguards is significant if IBC certification is not reviewed by NIH. The turn around time for ORDA review of an IBC assessment of a recombinant DNA activity is only 4-5 days.[2] Therefore, the delay to scientists seeking to begin a new or altered experiment is small. Because of these two reasons, EDF concludes that the public is better served by requiring NIH review and approval of IBC certification. EDF does suggest that the staff of ORDA be expanded to shorten the turn around time. Currently, 2 people at ORDA review IBC project certifications. If DHEW adopts these suggestions, the same procedure would apply to persons seeking to initiante new experiments in an ongoing NIH funded project.

IV-B. According to this section, all non-NIH funded projects, even those involving P-4 containment requirements, at institutions that are subject to the "Guidelines" may be initiated and altered solely on the basis of IBC approval. Notification of IBC action must be sent to NIH within 30 days of IBC approval. EDF takes issue with this procedure.

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[1] Dr. William Gartland, Director, Office of Recombinant DNA Activities, personal communication.

[2] Letter from Donald Fredrickson to Senator Edward Kennedy, May 22, 1978.

EDF suggests that both NIH funded recombinant DNA activities and non-NIH funded recombinant DNA activities at institutions subject to the "Guidelines" be treated in a similar procedural fashion and that experiments not be initiated or altered until NIH approval is received. A recombinant DNA experiment poses the same threat to the health or environment no matter who pays for the experiment. EDF suggests that each person seeking to start or alter a recombinant DNA experiment at an institution subject to the "Guidelines" be required to file with the IBC a project registration statement, containing information identical to that contained in a MUA. The IBC should then conduct the review and certification described in Appendix C, sections II-A-d and II-A-e. The registrations should then be forwarded to NIH. Within 5 days NIH should either approve the registration or specify the modifications necessary to bring the project into compliance with the "Guidelines". Experiments may be begun or altered upon receipt by the IBC of NIH approval. In cases where modifications are required, the experiment should be allowed to proceed after the IBC certifies to NIH that the modifications have been completed. If adopted, this procedure would also apply to persons seeking to initiate a project contained in a competing grant application to NIH before NIH completes its award procedure.

Respectfully submitted,

Leslie Dach

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Science Associate

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BRUCE J. BRENNAN
VICE PRESIDENT AND GENERAL COUNSEL

September 25, 1978

Donald S. Fredrickson, M.D.
Director
National Institutes of Health
Department of Health, Education and Welfare
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

This letter is in response to your request for comments on the proposed Revised Guidelines for Recombinant DNA Research, published in the Federal Register of July 28, 1978, (43 FR 33043).

The PMA and its member companies are pleased to note that the revised guidelines reflect a reasonable approach to Recombinant DNA Research and a further improvement of previous guidelines.

We support the added flexibility provided for in the guidelines. Particularly, we are pleased to note (1) the increased importance of institutional authority, (2) the mechanisms for lowering containment levels as experience is gained and (3) the exemptions provided for in the proposal.

In addition, the following specific comments and recommendations on the revised guidelines are offered for your consideration.

Sections IV-C-3&4 do not offer an adequate system for protection of patentable subject matter and other proprietary rights. For example, the suggestion that patents be applied for prior to disclosure to the NIH of experimental outlines is an impractical and unreasonable approach. There should be a more effective means for preserving proprietary/patent positions, which also affords the private sector the benefits of voluntary registration.

Also, the 10 liter volume restriction (Section I-D-6) would appear to apply to all categories of experiments (Section I-E), including those which have otherwise been exempted from the guidelines and NIH registration. This specific policy is unduly restrictive as written, though the implication may not be the intended meaning. This section also indicates that "appropriate levels of physical and biological containment" will be assigned

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upon granting of an exemption from the 10 liter restriction. This system places an unnecessary burden of uncertainty upon those developing processes destined for large-scale production. Clarification is needed. We suggest that a schedule for assigning containment levels to exempted large scale activities be developed to provide more certainty for planning research programs.

Finally, due to increased involvement of the Research Advisory Committee in decisions affecting industries potentially involved in large scale production, we would propose adding to the Committee's membership individual(s) with knowledge and expertise in the area of industrial microbiology and large scale production of microbial products.

We recognize that the NIH Guidelines do not apply to research conducted in private industrial laboratories; nevertheless, the spirit and intent of the guidelines has been, and should continue to be, followed by PMA member firms. If, at some time in the future, compliance with all provisions of the guidelines becomes mandatory for all laboratories involved in Recombinant DNA Research, certain procedures in the guidelines will pose a difficult problem in terms of patentability of new concepts and protection of proprietary interests. With the few exceptions discussed in our specific comments, compliance with other features of the guidelines appears reasonable.

We are pleased to participate in your efforts to improve the revised guidelines, and you have our assurance of continued cooperation and assistance in your excellent endeavor.

Sincerely yours,

Bruce J. Brennan

BRUCE J. BRENNAN

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JAMES H. SAMMONS, M.D.
Executive Vice President
(751-6200)

September 25, 1978

Donald S. Fredrickson, M. D.
Director
National Institutes of Health
Bethesda, Maryland 20014

Re: "Recombinant DNA Research, Proposed Revised Guidelines"; as published in the Federal Register on July 28, 1978 (43 F.R. 33042)

Dear Doctor Fredrickson:

The American Medical Association takes this opportunity to comment upon proposed revised guidelines for the conduct of recombinant DNA research that is either supported by the National Institutes of Health (NIH) or conducted at an institution where NIH supported recombinant DNA research is also being conducted. The proposed revised guidelines are designed to update and improve upon NIH's original recombinant DNA research guidelines published in 1976.

There has been a significant amount of activity concerning regulation of the way recombinant DNA research is conducted. This activity developed in response to concerns expressed by scientists and interested laypersons regarding the potential risks to the environment posed by recombinant DNA research. In the period prior to the issuance of the NIH guidelines, it was speculated that an accidental release or discharge of recombinant DNA organisms or possible "super pathogens" (resistant to known physical defenses and with no known natural antagonists) could endanger the environment or the whole human race. It was in this atmosphere that NIH imposed its initial guidelines. At that time, NIH fully intended to revise and restructure its guidelines as new information regarding the risks and the benefits involved in the recombinant DNA research became available.

The regulation of recombinant DNA research can be justified as necessary to protect the public health and safety. However, the regulation of recombinant DNA research, as with the regulation of any basic scientific inquiry, must not be allowed to become so

ponderous as to lessen initiative and motivation for the conduct of such work. Furthermore, regulation of recombinant DNA research should not become the precedent for regulating other areas of basic scientific inquiry. Therefore, NIH's guidelines should be kept to a minimum with sufficient flexibility to adapt rapidly to the needs of creative research endeavors.

We believe that these proposed revised guidelines are a substantial improvement over the original 1976 NIH recombinant DNA research guidelines. As the preamble to the proposed guidelines indicates, new information about the risks and the benefits of recombinant DNA research is becoming available at an ever increasing rate. More research is providing experience on techniques for both physical and biological containment of recombinant DNA molecules. In fact, certain of the scientists who originally expressed grave concern about recombinant DNA research and its potential impacts on the environment have indicated that their concerns have lessened based upon the experience of recent years.

Therefore, the increased flexibility at the local and at the national level to modify procedures under the guidelines is encouraging. We believe that it is appropriate to provide the Director of NIH with the flexibility to exempt certain recombinant DNA research from the guidelines as well as allowing certain prohibited research to take place after an individual case by case analysis of risks and benefits. We also believe that the reliance on local institutional bio-hazard committees is proper based upon their performance in supervising viral research.

The American Medical Association believes that regulation of basic research should be kept to an absolute minimum in order to prevent limitations on free inquiry and scientific freedom. When certain research presents an unusual risk of hazard to the public, only the minimum controls necessary to protect the public should be imposed. We believe that the proposed revised guidelines for recombinant DNA research meet this criteria. As new information becomes available concerning the risks and benefits of recombinant DNA research, we would expect continued modification to the guidelines to insure that they represent the minimum amount of control necessary to protect the public based upon the state of the art of recombinant DNA research.

Very truly yours,

James H. Sammons, M. D.

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U.S. DEPARTMENT OF LABOR
Occupational Safety and Health Administration
WASHINGTON, D.C. 20210

Office of the Assistant Secretary

SEP 25 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

This is in response to your request for Comments on the Recombinant DNA Research Proposed Revised Guidelines - NIH published in the Federal Register VOL. 43, No. 146 - July 28, 1978.

The comprehensive Occupational Safety and Health Act of 1970 (the Act) was designed to protect all working men and women, including, therefore, those whose employment involves biological research. While the Act covers all working conditions, it does not apply to those working conditions addressed by regulations issued by other Federal agencies under other Federal statutes whose purpose is to provide safety and health protection for employees. That exception is contained in section 4(b)(1) of the Act. However, section 4(b)(1) would not be involved in the case of the Guidelines, since they are not regulations promulgated under a statute whose specific purpose is to protect workers.

Federal, state and local governments are not defined as "employers" under the Act, and therefore, their employees are not covered. However, States operating under state legislation and enforcement plans approved by OSHA under section 18 of the Act, must, as a condition of such approval, cover State and local employees under the State plan. There are currently 23 States operating under such plans. In the remaining States, the guidelines perform an especially important function in protecting public employees in NIH-funded State institutions. For your further information, if an exempted State institution enters into a contract with a private employer to perform work for the State, that private employer is, of course, covered by the Act on the same basis as any covered employer.

As you are aware, the Occupational Safety and Health Administration (OSHA) does not currently have a specific standard governing the use of recombinant DNA. However, apart from the Act's requirement that employers comply with OSHA standards, the Act additionally imposes upon employers a general duty to assure that employment and places of employment are free from recognized serious hazards (sec. 5(a)(1)). OSHA is particularly interested in the Guidelines in that they may prove helpful in identifying recognized serious hazards. In any event, guidelines are an additional means of providing protection for those engaged in work under a grant program.

In an effort to provide broad input to the revision of the Guidelines which were first issued on June 23, 1976, the NIH has coordinated the contributions of both the scientific and public communities in drafting the PRG's. In this way, OSHA has followed the revision of the Guidelines with great interest. We continue to actively participate in the study of federal regulation of this technology through our membership on the Interagency Committee on Recombinant DNA Research. As outlined at these meetings, our primary concern is to insure that workers involved in this research are adequately protected under Federal guidelines, and that they are applied uniformly in all workplaces engaged in recombinant DNA research. In view of our established concern in this area, I submit the following comments concerning the PRG's.

- The Guidelines state certain general principles, the first of which is that certain experiments may be judged, in the light of currently available information, to present such serious potential hazards, that they should not be attempted at the present time. This principle specifically states six prohibited experiments. A major proposed revision would give the Director of NIH the authority to grant exceptions to any of the six prohibitions, based upon the recommendation of the Recombinant DNA Advisory Committee (RAC). At the present time, OSHA is not represented on the RAC and would want to render advice to the Director should a waiver of a prohibition be considered. Two areas are of particular concern to us: exceptions from any section for the purpose of risk assessment; and exceptions from Section I-D-6, which prevents large-scale experiments over 10 liters of culture. I urge you to require consultation with relevant research and regulatory agencies prior to the granting of any exceptions.

- The PRG's include a new section entitled "Exemptions," which lists five types of experiments which would be exempt from the Guidelines and for which no registration with NIH

is necessary. Section I-E-4 would exempt certain recombinant DNA experiments on the basis of genetic exchange. It is not clear what scientific information is required for inclusion on this list, nor what administrative procedures will be followed to assure public participation in future additions or deletions. I suggest that prior to any decision, NIH make available to the public any experimental evidence which documents genetic exchange, and that such exemptions should be listed as pairs of exchangers by species, and not genus as is currently proposed.

- Section II-A of the PRG deals with Standard Practices and Training, for the purpose of containment. Containment is dependent on good microbiological techniques as much as technological or biological controls. Both the Guidelines and the PRG's require "adequate instruction." I suggest that you develop a specific curriculum to be followed in the training of recombinant DNA workers and require certification that this training has taken place for each worker.

- The current Guidelines prohibit mouth pipetting at the P2, P3, and P4 levels of physical containment, but it is allowable at the P1 level. I commend you for your decision in the PRG's to ban mouth pipetting at all containment levels as this greatly improves the concept of safety at the P1 level.

- Part IV of the 1976 Guidelines, Roles and Responsibilities, provide the administrative framework for implementation of the Guidelines. This requires that the Principal Investigator assess any potential biohazards, institute appropriate safeguards and procedures and prevent accidents and illnesses. Where research is conducted at a P3 or P4 level, there must be a Biological Safety Officer who must verify training, inspect for compliance with safety standards, develop plans for dealing with accidental spills and personal contamination, investigate accidents, review medical effects on the personnel, and provide advice on laboratory security. Each institution must have an Institutional Biosafety Committee (IBC) to give advice on policies, to create and maintain a central reference file, and to develop a safety and operations manual for any P4 facility.

The PRG's give increased local authority for implementation of the guidelines. The local biosafety committee has also been given the primary responsibility for the review, determination of containment levels, and approval of initiation of all recombinant DNA research at that facility. I feel that too much responsibility for interpretation and enforcement has been placed at the local level. I anticipate many

problems with this structure, especially if the Guidelines were applied to the private sector as would occur if pending legislation is enacted.

I have several specific suggestions for improvement of this Section.

- Membership on the IBC or Area Biosafety Committee (ABC) should specifically be mandated to include significant worker representation and public membership. I also suggest that you urge consideration of members from disciplines in addition to the biological sciences, e.g., engineering and chemistry.

- Additional emphasis should be placed on the emergency plans to be developed by the Biological Safety Officer. I suggest the addition of a requirement for a team of experts "on call" to handle emergency situtions. This team should include, among others, a medical officer and an engineer knowledgeable of physical and chemical containment.

- The PRG's state that it is the responsibility of the Institution to "determine, in connection with each project, the necessity for medical surveillance of recombinant DNA research personnel..." In view of the fact that the effects of exposure are unknown, we suggest a requirement for biological monitoring of all exposed personnel.

- Too much responsibility lies with the Principal Investigator. Perhaps the Biological Safety Officer should share this primary responsibility for enforcement. To accomplish this, an independent Biological Safety Officer, not engaged in such research, should be required at <u>all</u> levels of containment (not just at the P3 and P4 levels). He or she should have a background in occupational or environmental safety and health as well as microbiology. Such a position is important to insure strict enforcement of procedures and monitoring of personnel, especially at the lower levels of containment where technique is so important. Standardized inspection reports should be filed with NIH in order to insure enforcement.

- Under the PRG's, NIH notification is not required before research can begin. That is, once a local IBC or ABC has approved a specific experimental protocol and determined the level of physical and biological containment that it requires, the project may proceed without a second review at the federal level. I urge you to require such notification to strengthen your control over the uniform interpretation and enforcement of the guidelines.

Under Section IV, the RAC is charged with the responsibility for recommending revisions of the Guidelines, recommending the certification of certain host-vector systems which meet established criteria, resolving questions concerning potential biohazards and adequacy of containment, and recommending exemptions from specific requirements. The PRG's state that NIH is considering additional public members on the RAC and that you are formalizing the procedures for the selection of such members. I recommend that you consider more public members, as well as members representing other scientific disciplines such as epidemiology, ecology, environmental health, and risk assessment.

Because of our agency's role in worker protection, we have attempted to follow the development of the Guidelines. We have a strong interest in the Guidelines as well as their interpretations. To facilitate this, I recommend that OSHA be named as a full member, or as a Liaison Representative to the RAC such as those from other Federal agencies. Our representation should also be of benefit to NIH, as you will will soon be handling research protocols from the private sector, including proprietary information from industry.

The "Laboratory Safety Monograph - A Supplement to the NIH Guidelines for Recombinant DNA Research" is a very well-written and valuable addition to the Guidelines. However, since it is the intention of NIH that the procedures outlined in this book be followed to insure the integrity of the Guidelines, I urge that the provisions be mandatory rather than advisory in nature. In this way, strict enforcement and uniform interpretation of the procedures can be guaranteed. In the event that the special conditions of a facility warrant different procedures than those outlined in the Monograph, NIH could grant such a waiver following your review of the alternatives proposed.

You state on page 33128 that grievance procedures for workers under the Guidelines were requested but "not considered necessary, as the rules and regulations of the Occupational Safety and Health Act already provide such a mechanism." You are correct that the Act would apply in most situations and that a worker's right to file a safety or health complaint is provided for under that Act. The Act also provides that no employee may be discriminated against for exercising his or her rights under the Act. However, as stated earlier, the OSH Act does not cover employees in State or local government institutions, unless that State has a State plan approved by OSHA. Since only 23 States have such plans at this time, it

is conceivable that employees in some NIH-funded State institutions would not be protected. I, therefore, urge you to include in the Guidelines procedures for employee complaints and protection against employee discrimination for using the procedures. The employee complaint mechanism is one which encourages compliance with good safety and health practices and would be a valuable tool in insuring compliance with the Guidelines. I will be happy to provide staff assistance in drafting such provisions if you desire.

I thank you for the opportunity to comment on these proposed revisions and look forward to the promulgation of the final Guidelines.

Sincerely,

Eula Bingham

Eula Bingham, Ph.D
Assistant Secretary
Occupational Safety and Health

Science for the People

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September 25, 1978

Dr. Donald Frederickson
Director, NIH
Bethesda, Maryland 20014

Comments on the proposed revised guidelines for recombinant DNA research.

There are three sections to these comments. First, specific safety procedures which should be instituted--including a requirement that workers on antibiotic therapy not be allowed into recombinant DNA laboratories--are described. Second, the scientific justification of the guidelines are discussed. The document lacks a clear statement of the hazards and it makes changes in experimental containment that have not been based on adequate discussion among scientists and other interested parties. Last of all, there are some changes that should be made in the section of the guidelines on "Roles and Responsibilities".

The effects of antibiotics in promoting the spread of plasmids and bacteria carrying genes for antibiotic resistance is well known. The guidelines should explicitly prohibit those who are receiving antibiotic therapy from working in recombinant DNA laboratories, until seven days after the end of treatment. This concern was expressed in the original (june 1976) guidelines, and received scientific support from two participants at the Falmouth conference (1,2). The alteration of normal gut flora by antibiotic treatment might also contribute to the spread of chimeric plasmids.

The Scientific Advisory Board of the EPA recommended strongly that all bacteria used in recombinant DNA experiments be tagged (3) so that their spread, after a spill, could be detected in the environment. Although this is not easy to carry out in practice, the possibility should be considered by the NIH. Spill or no spill, however, an important preventive measure is needed to guard against one possible first step in the escape of a recombinant DNA vector. Cultures of the HV1 host E. coli K12 (as an example) may be contaminated with wild-type or other vigorous strains of E. coli being studied in the same or neighboring labs. E. coli containing a transferable R-factor can mobilize non-transferable plasmids from E. coli K12 in vitro (4). This is more likely than transfer in the intestine, for example. Because of this possibility of in vitro contamination and transfer, testing of the purity of HV1 and HV2 host-vector systems should be a required part of recombinant DNA work. Although methods have been described for testing the purity of E. coli K12 and other certified bacterial strains for the research their use should be required in the guidelines' section on biological containment.

A revision of paragraph I-D-5 of the revised guidelines is required. As written, it does not exclude the possibility of giving to some pathogenic organism a drug resistance which it might acquire only extremely rarely in nature. The emergence of a penicillin-resistant strain of gonorhea was a rare but naturally occurring event that has posed serious medical problems. Nowhere do the guidelines prohibit the repetition of a similar experiment in the laboratory. Section I-D-4, prohibiting the release of such an organism into the environment, is not an adequate safeguard.

The educational value of the guidelines (which is important in addition to their regulatory value) is hampered by not having a clear statement of the dangers of recombinant DNA research. In addition, the scientific basis for reductions in containment often appear obscure or arbitrary. For example, the containment of shotgun experiments with primate DNA has been lowered from P4/EK2 to P2/EK2. The rationale for this, stated in the director's introduction to the guidelines, is that the possible hazards of cloning viral DNA, which is known to be inserted in primate DNA, have been re-evaluated and are considered less serious. The basis of this was the Ascot workshop on viruses held in January 1978. The fact that this conference was open to only a carefully selected group of scientists, and that a summary report could not possibly consider many of the questions about the safety of cloning viruses which were certain to have been raised there, is not reassuring. Such critical debates should not be held outside the eye of interested participants such as Science for the People, union or environmental groups, much less the Recombinant DNA Advisory Committee (RAC), losing here its role in originating containment guidelines. Other hazards of experiments on primate DNA are not evaluated(5).

One possible hazard of recombinant DNA technology, that recombinant organisms can generate autoimmune diseases in humans (6), should be given more attention in a more open scientific forum than the Ascot conference. An autoimmune disease might result from the exposure of a human protein in an altered state (on the surface of a bacterium) and the subsequent activation of a human's immune system that might lead it to attack the same protein elsewhere in the same person. A reason for concern is that the human intestine does not provide a perfect barrier for proteins which might pass through it. It is very likely that mature adults regularly absorb macromolecules (proteins) from their intestine. A recent scientific study on lactating mothers strongly supports this possibility (8):

"Our clinical findings strongly suggest that some factor or factors in cow's milk produces colic in infants. ((Our experiments suggest)) . . . that a macromolecular substance eaten by the mother enters her breast milk. There is increasing evidence that the normal intestine is permeable to macromolecules in quantities that might be antigenic or biologically active(7)."

One can imagine that large scale production of specific human proteins, at the P2/EK1 levels the revised guidelines would permit, might conceivably bring about an immune response as well as some resulting disease in those working with the strain. The bacterial synthesis of large quantities of insulin, as is already being undertaken, is one case where this might occur in the near future. Exposure to an altered human protein might not only occur via the intestine. An EK1 host (namely E. coli K12) producing human proteins, reaching the bloodstream after penetrating the skin accidently, might persist in the body for several days. This has been shown for a strain of E. coli K12 injected into mice (9). The length of time during which the autoimmune response develops may enhance the seriousness of the resulting disease.

Individual academic or industrial laboratory workers will be the first to discover the hazards of autoimmune diseases, not the general population. It is a hazard of the workplace and not an epidemic hazard. The NIH has not given serious consideration to this problem.

The NIH role in developing and changing thse guidelines needs to be examined. First, will the guidelines be altered from now on, piece by piece, at the NIH director's discretion, with no possibility for further public hearings? Second, many scientists still have important concerns about the safety of the research. Nominations to the RAC, and the qualifications of the nominees, should be openly discussed. A final requirement for active, informed, public participation--all institutional biohazards committee meetings whould be open to the public. It is not enough that the minutes alone be available for public inspection. Furthermore, representatives of non-doctoral, technical staff should be required as members of the IBC's. Local community representatives should have their nominations to the biohazards committee ratified by local community governments.

Thank you for your interest in these comments. I am a member of Science for the People and the Coalition for Responsible Genetic Research, but do not represent the opinions of either group. I have benefitted greatly from discussions with members of both in analyzing this issue. I am also a graduate student in the Biochemistry Department at Harvard University.

Scott Thacher

Scott Thacher

copies to:
Donald Federickson, NIH
Peter Libassi, NIH
Douglas Costle, EPA
Eula Bingham, OSHA

(references follow)

Comments on the NIH guidelines -- References

1. R. Curtiss III, Biological Containment and Cloning Vector Transmissibility. J. Inf. Dis. 137, 668 (1978)

2. S. B. Levy, Emergence of Antibiotic Resistant Bacteria in the Intestinal Flora of Farm Inhabitants. J. Inf. Dis. 137, 688 (1978)

3. Letter to Dr. Emil Mrak, EPA, from Martin Alexander, Ad Hoc Study Group on recombinant DNA policy, Science Advisory Board, April 28, 1978

4. E.S. Anderson, Plasmid Transfer in E. coli. J. Inf. Dis. 137, 686 (1978)

5. A speculation -- footnote #13 in Frederickson's introduction-- is that major structural features found in all genes of higher organisms and not bacteria will prevent the full expression of eukaryotic genes in an E. coli host. The universality of these structural features can hardly be be inferred from the limited data now available. Furthermore, it is easy to see how biologically active material could in any case be produced from portions of these cloned eukaryotic genes.

6. J. King, Recombinant DNA and Auto-Immune Disease. J. Inf. Dis. 137, 663, 1978

7. Walker and Isselbacher, Gastroenterology 67, 531 (1974)

8. I. Jakobsson & T. Lindberg, Cow's Milk as a Cause of Infantile Colic in Breast-Fed Infants. The Lancet 26 August 1978, p. 437

9. S.B. Levy, N. Sullivan, and S. L. Gorbach, Pathogenicity of conventional and debilitated E. coli K12. Nature 274, 395 (1978)

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Dr. Donald S. Fredrickson
Director
National Institute of Health
Bethesda, MD 20014

September 25, 1978

Dear Dr. Fredrickson:

We submit for your consideration the comments of the Consumer Coalition for Health on the proposed revisions in the Recombinant DNA Research Guidelines.

The Coalition's comments focus upon issues of public participation in decision-making. Because these issues recur throughout the health system and because they are so central to the purposes of the Coalition, it has adopted an official public participation policy, and directed its officers to effectuate that policy. The enclosed comments are submitted pursuant to that directive.

In addition, we would like to add on our own behalf as individuals a comment regarding section IV-D-1, which deals with enforcement of the Guidelines. Our suggestions stem from considerable experience regarding enforcement problems, and we hope that you may find them useful.

The only enforcement mechanism which NIH appears to have considered is the possibility of suspending, limiting, or terminating research funds to non-complying institutions. Fund termination is an essential but inherently inflexible remedy which is at once too strong and too weak to carry the full burden of enforcement. On the one hand, it is a drastic sanction which often hurts not only the recipient of federal funding but also the public interests that funding was designed to serve. As a result, some violations which are significant and may be dangerous but which are not thought sufficiently grave to warrant termination, may be allowed to continue without any sanction whatever.

On the other hand, fund termination and specific enforcement proceedings are too weak in that they are purely prospective in effect. NIH concedes that it does not have the resources to effectively oversee compliance, and that primary enforcement responsibility must be placed on the recipient institutions themselves. Assuming, however, that violators will be given an opportunity to come into voluntary compliance before enforcement

proceedings are initiated, recipients may be inclined to sit back and wait for NIH to uncover violations; they will have little incentive to seek actively to uncover and correct non-complying practices themselves. In order to provide that incentive, NIH should consider revising its MUA to provide for retrospective relief and damages. For instance, an institution could be permitted to receive prospective funding but required to reimburse NIH for all or part of the federal monies expended during the period in which it was out of compliance. Similarly, in those cases where fund termination is selected as an appropriate remedy, the non-complying institution could be required to provide NIH with the results of research already conducted, and to pay for setting up additional facilities and replicating experiments elsewhere. Regardless of whether NIH has the authority to impose fines without additional legislation, it clearly has the authority to enter into contracts which provide that its grant of funds is contingent upon compliance, and which permit it to seek reimbursement for any funds expended upon activities not conducted in accordance with contractual assurances.

We urge that HEW consider specific performance and retrospective remedies, rather than limiting its enforcement arsenal to a single inflexible and inadequate enforcement weapon.

Sincerely yours,

Sanford A. Newman, Attorney
Herbert Semmel, Attorney
Deborah Agus, Student Intern

Enclosure

SAN:vl

cc: Peter J. Libassi,
General Counsel

Consumer Coalition for Health
"Consumers United for Better Health Care through Effective Planning"

1511 K Street, N.W., Suite 220
Washington, D.C. 20005
202/347-8088

Dr. Donald S. Fredrickson
Director
National Institute of Health
Bethesda, MD 20014

September 25, 1978

Dear Dr. Fredrickson:

The procedures for public participation contained in the proposed revisions of the DNA recombinant research guidelines are woefully inadequate. The impacts of this research, both beneficial and deleterious, can be expected to have a tremendous impact on the public. Nearly all major decisions involving DNA research involve two principle components: (1) technical assessment of potential risks and benefits which may flow from alternative decisions; and (2) balancing of the identified potential risks and benefits in light of social values to determine which alternative should be selected. Nevertheless, the proposed guidelines would leave both the technical and value-oriented components in the hands of scientists and others selected by research institutions -- people whose personal interests and professional roles are likely to lead to incomplete and one-sided consideration.

While research scientists share equally in the stake which all of us have in public safety, they can hardly be expected to attach the same weight as others to potential benefits and dangers of research. They have often chosen their profession precisely because they attach preeminent value to increasing the store of human knowledge, and they have been taught to emphasize that value throughout their professional training. Scientists associated with research institutions are likely to perceive this responsibility as the quintessential characteristic -- indeed the very raison d'etre -- of their professional roles. Fame and acclaim come not from efforts to ensure that experiments are conducted in ways which maximize safety, but from breakthroughs in scientific understanding. While research scientists as a group can undoubtedly be proud of the strenuous efforts frequently made to ensure that experiments will not endanger the public safety, their professional perspective will often lead them to focus most sharply on their responsibilities to

facilitate important research, leaving the problems of safety slightly blurred at the edge of the picture. Moreover, scientists may feel a little less anxiety than others about the need for stringent controls over themselves and their colleagues. Good faith efforts objectively to evaluate potential safety problems and benefits can hardly be expected to overcome such deeply held values or years of habit in approaching research problems from a particular perspective.

It is obvious that the technical expertise which scientists can offer must be heard in any discussion about DNA research procedures. But it should not be permitted to drown out the equally important contributions of those who approach the discussion from different perspectives. Dissent and disagreement are vital tools for ensuring that all aspects of a problem are seen and evaluated. If we are to provide a mechanism for fully-informed decision-making, we must see that the inherent biases and normative predilections of the scientific research community are balanced against those of others. If we really believe that all citizens should have the opportunity to influence decisions which may have a vital impact on their lives, the guidelines must be changed to provide for meaningful public participation at each stage of the decision-making process.

I. INSTITUTIONAL BIOSAFETY COMMITTEE (IBC)

The proposed revisions concentrate in the IBC a great deal of power and a great responsibility to make both technical and value judgments affecting all members of the community.

Nevertheless, the Guidelines substitute meaningless tokenism for meaningful public composition and vague lipservice for substantial guarantees of open proceedings.

Composition

The Guidelines regarding IBC composition require only that one member must be someone not affiliated with the recipient institution. They recommend, but do not require that one member be a non-doctoral person on the laboratory staff, and provide that no member may review "a project in which he or she has been or expected to be engaged or has a direct financial interest."

These provisions are at best naive and unrealistic. In the first place, all of the problems of role and perspective which make it inadvisable to entrust non-technical policy considerations entirely to research scientists are exacerbated when the scientists

to whom the task is entrusted are affiliated with the recipient institution. Provisions prohibiting participation by those with a "direct financial interest" cannot obscure the fact that the entire institution may stand to benefit, either financially or in terms of reputation, from the research under review. The interests of the institution, with which its staff can be expected to identify and to which they are accountable, cannot by any stretch of the imagination be equated with the interests of the public. Moreover, few people -- even people with scientific training -- are so far beyond human frailty that they can be expected to serve as objective and rigorous reviewers oblivious to the personal interests of their co-workers and friends, and to the institutional interest of the laboratory with which they are associated. These considerations point forcefully to the conclusion that even the scientists on the IBC should be appointed by some authority outside the recipient institution.

Secondly, allocation of one vote to a non-institutional representative may be a symbolic nicety but can hardly be expected to provide the IBC with balance and objectivity. Such a half-hearted nod to the principle of public participation is nothing more than an empty gesture -- a gesture which ignores both the broad diversity of community views entitled to representation and the political reality that a lone outsider will have little influence and less power and may be quickly cowed into comformity and quietude. Moreover, since there is no limit on the number of IBC members, even the minimal impact of the non-institutional member on a five-member committee will be further diluted where the size of the IBC is increased.

Furthermore, even the non-institutional member is to be appointed by the institution. The friends and acquaintances of the selectors are unlikely to constitute a broad cross-section of the communities. More fundamentally, it will be the rare institution which will appoint someone expected to pose a serious challenge to institutional policies or perspectives. Thus the present guidelines do not require a single public representative. They require only that one of the institution's representatives be someone not directly affiliated with the institution. Meaningful representation requires that representatives be chosen by and accountable to the constituency they represent. Serious consideration should be given to prohibiting the institution from appointing more than a single representative to the IBC.

We strongly urge the adoption of the following changes in the proposed guidelines:

(1) The IBC should have a minimum of seven members. Any smaller number is simply insufficient to permit adequate representation of the diverse elements entitled to a voice in decisions regarding DNA research. The requirement for public representation

on the IBC must be expressed as a percentage of total membership, so that it will not be diluted as the committee grows in size.

(2) Serious considerations should be given to providing that the institution may appoint only a single representative to the IBC, and that even scientific representatives must be appointed by some other authority or panel. Even if this suggestion is rejected, the institution should be permitted to appoint no more than 3/7 of the IBC members. One of these three should be required to be selected exclusively by non-professional institutional employees.

(3) In order to assure adequate public representation and to assure that public representatives will be accountable to their constituency, the guidelines should provide for appointment of at least 4/7 of the IBC members by elected public officials, subject to confirmation by the appropriate legislative body.

(4) In order to assure that diverse interests and perspectives are represented, the regulations should further provide that the public representatives must include at least one representative of an environmental organization, one representative of a local public health agency, and one consumer member of the local Health Systems Agency. Moreover, the institution should be required to notify the local HSA immediately upon filing any application for federal funds for recombinant DNA research.

Voting and Reporting

Although nearly all the decisions IBCs will make will involve technical and non-technical components, some will be less technical and more policy oriented than others.

A voting system which permits institutional or scientists representatives to exercise 3/7 control over all decisions means a unified institutional or scientist bloc will prevail every time they are able to convince one out of four public representatives to go along with them. Such extraordinary power is proper only on issues which are unusually technical and arcane, if it is ever appropriate at all. On all other issues, decisions should require majority public member support or at least a 2/3 vote of the IBC. It may be possible to define in the Guidelines certain categories of decisions, such as the decision to undertake a particular research project, which clearly entail large social-policy components, and therefore sould require majority public representative support. For other issues, a 3/5 vote of the IBC should be required to categorize a decision as a "technical" decision requiring less than majority public representative support.

Open Meetings

The decisions of the IBC are sufficiently critical that all meetings should be open to the public. The Guidelines include no requirement that meetings be open, apparently because of the possibility that some portions of some meetings may involve discussion of proprietary information. See 43 Fed.Reg. 33065. Although the Decision of the Director does "urge ... that local committees, when possible have open meetings and suggest that all meetings be announced," ibid, even these suggestions find no place in the proposed Guidelines.

Regardless of whether HEW chooses to allow researchers to obtain patents on the results of NIH-funded research, it clearly has the authority to condition grants of federal money on agreement that all IBC sessions will be conducted in public. We question whether the interest in protecting proprietary information is sufficiently compelling to justify shrouding important IBC decisions in the secrecy of closed sessions.

Moreover, it is absolutely clear that a decision to protect proprietary information cannot justify closing to the public those meetings at which no such information is presented. The Guidelines should require at a bare minimum that all IBC meetings be open to the public unless the committee votes to close a limited portion of a particular meeting at which proprietary information is to be discussed.

Moreover, the Guidelines should specify procedures by which each IBC must provide public notice of the date, time, place and agenda in advance of its meetings.

II. RECOMBINANT DNA ADVISORY COMMITTEE

The responsibilities of the RAC, even more than those of the IBC's consist largely of balancing competing social policies and values. Decisions to revise guidelines, to certify host vector systems to establish exemptions or to permit exceptions to prohibited classes of experimentation can hardly be characterized as purely or even predominately technical in nature. Accordingly, it is imperative that the proposed Guidelines be revised to provide adequate public representation on the RAC and adequate opportunity for public comment at all stages of the decision-making process.

The Decision of the Director indicates that the RAC currently includes two public members, that they "have served the public interest well and have done a superb job," and that more public members "may be added." Despite this recognition of the important role of public representatives, neither the decision document nor

the Guidelines themselves contain any requirement that the RAC include public members, much less any information about the basis upon which such members will be selected. Moreover, the concept of a separate public advisory committee has been rejected on the premise that the DAC adequately meets the need for public participation at the national level. This premise misconstrues the role of the DAC, ignores the realities of the deicsion-making process, and subordinates the public interest to the tyranny of technical expertise.

There can be no question that the RAC is the principal advisory body on recombinant issues. The DAC, with responsibilities over a broad range of subject matter, has neither the time nor the mandate to immerse itself in any but the most far-reaching of DNA research decisions, and cannot focus on even those decisions in the same depth as the RAC. Its members cannot be expected to develop the same range or depth of knowledge regarding complex DNA research issues as could public members who were included in ongoing oversight and continuing evaluation on the RAC.

Moreover, DAC review comes at a very late stage of decision-making. As a result, its contributions will ordinarily be incremental and reactive, and the opportunity for constructive and creative interaction between public and scientific members is likely to be lost. Because the timing of participation in decision-making processes is so often crucial, there must be full public participation at each critical stage of that process.

The Guidelines should be revised to include a requirement that a majority of the RAC consist of public representatives, and to assure that both scientist and lay members of the Committee reflect a balanced view of the public interest. Although additional consideration should be given to the particular constituencies and proportions which would best serve this purpose, the following model may provide a useful starting point: One third of the scientist members and one third of the lay members would be selected from among persons nominated by environmental organizations. The remaining two thirds would be selected from among persons nominated by the Environmental Protection Agency, NIOSH, the Center for Disease Control, an organization of research scientists, and an organization representing non-professional laboratory employees.

In addition to these changes regarding the composition of the RAC, we urge that the guidelines be expanded to include detailed procedures for public notice and comment in advance of RAC decisions.

Sincerely yours,

Herbert Semmel
President

Mark Kleiman
Executive Director

HS:vl
cc: Peter J. Libassi

NORTHWESTERN UNIVERSITY
EVANSTON, ILLINOIS 60201

DEPARTMENT OF BIOLOGICAL SCIENCES

September 25, 1978

Dr. Donald Frederickson
Director
National Institutes of Health
Bethesda, Md. 20014

Dear Dr. Frederickson:

We are writing to encourage you to approve the proposed Guidelines for Recombinant DNA Research as published in the Federal Register vol. 42 no. 187, September 27, 1977. The three of us are young scientists who have recently set up our own laboratories. We work independently, but we share a common interest in the organization and regulation of genes in higher cells, and we all use recombinant DNA procedures in our research.

The proposed revisions of the Guidelines will reduce to the P-2 level of containment, micro-organisms containing DNA from non-primate animal cells. Since two of us work with vertebrate DNAs, the Guidelines will affect us directly. The argument can be made that, even in the absence of demonstrated hazard from organisms containing recombinant DNA, the prudent step is to retain stringent containment as an added precaution, and as an example of scientific responsibility. We would like to argue, on the other hand, that the retention of P-3 containment conditions for non-primate DNA will serve as a major impediment to research by young investigators like ourselves.

The cost of implementation of P-2 containment is not extreme. We now have a limited access room with all necessary equipment which we have had renovated and furnished with funds at our disposal. The total cost for this research facility was about $10,000. The cost of a P-3 facility is, by our standards, staggeringly high; in excess of $50,000. This amount of money for renovation is seldom available to young scientists. The result is that work at Northwestern on DNA from vertebrates, except for work on a few characterized clones, will stop. Experimentation of this sort will become concentrated in institutions with large laboratories headed by more established scientists. Other individuals who are now graduate students or post-docs with interests in recombinant DNA research will then be encouraged to remain in such large laboratories, rather than starting out on their own, professionally and intellectually.

We do not feel that it is necessary or wise to remove all restrictions on recombinant DNA research. However, the Guidelines as now exist are unrealistically stringent. The proposed revisions seem to us to be a well considered and timely compromise. We urge your approval.

Yours sincerely,

Brian B. Spear
Assistant Professor
Biological Sciences

Jeffrey L. Doering
Assistant Professor
Biological Sciences

J. Douglas Engel
Assistant Professor
Biochemistry and
Molecular Biology

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Dr. Donald S. Fredrickson
Director, NIH

DATE: September 25, 1978

FROM : Dr. Philip Leder
Chief, Laboratory of Molecular Genetics, NICHD, NIH

SUBJECT : Proposed Revised Guidelines on Recombinant DNA Research

1. The proposed revision of the Guidelines on Recombinant DNA Research is long overdue and in the right direction. Unfortunately, even the Revised Guidelines continue restrictions that I feel are excessive and scientifically unjustified.
2. Specifically, the Guidelines that make the most sense are those that key restrictions to those employed in handling the most dangerous component of any given experiment. For example, if an experiment were being carried out with an organism that produces a toxin, the containment should reflect the containment necessary for that pathologic organism. All our expectations lead us to conclude that the recombinant would be less and not more dangerous than the original pathologic organism.
3. While many of the regulations do not add to the safety of what are basically safe experiments, they do serve to inhibit the development of new and versatile vector systems. In our own case, we have simply not attempted to develop additional vector systems because the redundant safety testing program is too onerous, time-consuming and, in our opinion, not scientifically justified. There are many modifications of vector systems that could increase their versatility,

but these are not being made because of the difficult and arcane procedure necessary to put these vectors into use.

4. Given an imperfect but improved set of Guidelines, I am particularly concerned about our inability to use physical containment in place of biological containment. For example, certain modifications of the bacteriophage λ might considerably increase its usefulness as a vector. This is true of plasmid vectors as well. None of these could be introduced and used without an elaborate clearance process under the revised Guidelines. At the very least, EK1 vectors should be available for shotgun experiments using the DNA of higher organisms if a P3 facility is used. In short, the revised Guidelines represent an improvement. But they still fail to make good scientific sense. I am afraid that this limitation will prevent their adoption as an international standard for the conduct of this research. The consequences of this will be to put research in this country at a decided disadvantage, without preserving for ourselves any advantage with respect to safety.

HELIOS JOSEPH HERNANDEZ, II
Attorney at Law

888 N. MAIN STREET, SUITE 417
SANTA ANA, CALIF. 92701
TELEPHONE (714) 558-0365

Sept. 25, 1978

Joseph G. Perpich, M.D., J.D.
Assoc. Director for Program Planning and Evaluation
National Institutes of Health
Building 1, Room 137
Bethesda, Md. 20014

Dear Joe:

My overall impression of the NIH Guidelines for Recombinant DNA Research is very favorable. They are an appropriate response to a difficult situation. As Federal regulations go, the Guidelines are brief and readable. My comments follow, and although they may seem critical, I want to emphasize that the vast majority of Guidelines are well done.

I. SCOPE

Section I.C., third paragraph is not clear. I suggest that you insert here the paragraph from page 33045, middle column, second full paragraph, Part IV of the July 28, 1978 Federal Register.

Section I.D. and I.E. are confusing. I.D. contains some exemptions which are identified as exceptions and I.E. contains exemptions. These two sections should be reorganized. Also, I think this is the place for a statement on risk assessment experiments. Further, there should be a statement here on experiments not explicitly covered by the Guidelines. In such cases the Director, after receiving appropriate advice, allow or disallow such experiments. If the experiment(s) is allowed, the Director should be empowered to set such conditions as are deemed appropriate.

II. CONTAINMENT

Section II.B. which states physical containment requirements is too wordy. For example, at P3 containment the requirements are all P1 and P2 requirements plus additional P3 requirements. The P3 requirements must, of course, be specified. There is no need to repeate those for P1 and P2 since they appear immediately before the subsection on P3 requirements.

Section II.C. should specify record keeping requirements.

III. GUIDELINES

By way of general comment, the tables are informative and much easier to read than the body of the narrative. The overall document could use a few more such devices to break up the mass of small type.

IV. ROLES AND RESPONSIBILITIES

I support the name change to Institutional Biosafety Committee. This modification more accurately reflects the intent of the Guidelines. A specific suggestion for IV.A.4.f. -- incorporate the material cited in the second paragraph of this letter. Overall, Section IV is a well done and worthwhile part of the Guidelines.

APPENDICES

My only comment here is that Appendix C is a very necessary part of the Guidelines. In Section I of the Guidelines there should be a brief mention of each of the appendices. In regards to Appendix C, it should be stated in Section I that Appendix C is mandatory.

ENVIRONMENTAL IMPACT ASSESMENT

After having, thoroughly read all of the documents pertinent to the Guidelines and the EIA, I am convinced that the environmental impact of recombinant DNA technology will be, on balance, highly beneficial. And in comparison to other existing technologies, DNA work has relatively little adverse impact.

LABORATORY MONOGRAPH

Due to the breadth and depth of this monumental work I have only skimmed it. The parts that I have read thoroughly are quite well done.

Sincerely,

H.J.Hernandez II

September 26, 1978

Re: Recombinant DNA Research,
Proposal for Revised Guidelines

Dear Drs. Fredrickson & Hartland,

While it appears to my layman's eye that most changes called forth by the proposed guidelines will minimize the hazards of this research, and that you are genuinely interested in minimizing these hazards, I can not condone the proposed guidelines. Hazard is inevitable in genetic engineering, as both an extension of human ethics and as a tool by which the normal proceedings of evolution are intentionally invaded and altered. And, indeed, to allow even "20 microorganisms" to escape from containment cabinets is to allow twenty too many.

Sincerely, Nancy Tilley

Nancy Tilley, Burns Rd., Wallack's Pt., Stamford, Ct.

MEMORIAL SLOAN-KETTERING CANCER CENTER

1275 YORK AVENUE, NEW YORK, NEW YORK 10021 (212) 794-6005
(212) 794-7541

September 26, 1978

Dr. Donald S. Fredrickson
Director,
National Institute of Health
Building 1 room 124
900 Rockville Pike
Bethesda, Md. 20014

Dear Dr. Fredrickson:

I have read the revised guidlines for DNA recombinant research and wish to express my support and appreciation for your efforts in this area of medical research.

As an investigator in human genetics, I have a deep interest in seeing that these studies continue with due consideration to safety measurements. In my opinion, the new guidelines, as they have been developed, fulfill these goals.

The fact that genetic research now allows us to realistically speculate that genetic defects can be corrected at the chromosomal level has made DNA recombinant research an important area to persue. Unfortunately, this has to some extent, been misinterpreted by the public and by some scientists. The new guidelines do, however, in my opinion, assure the public and the scientific community that such research can continue safely and rapidly.

Sincerely yours,

BD/lsh

Bo Dupont, M.D.
Professor of Biology
Cornell Graduate School
of Medical Sciences
Member, Sloan-Kettering Institute
for Cancer Research

[A-388]

MEMORIAL HOSPITAL FOR CANCER AND ALLIED DISEASES
SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
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MEMORIAL SLOAN-KETTERING CANCER CENTER

1275 YORK AVENUE, NEW YORK, NEW YORK 10021

September 27, 1978

Dr. Donald S. Fredrickson
Director
National Institute of Health
Bethesda, MD 20014

Dear Dr. Frederickson:

I would like to express my support of your attempt to revise the NIH Guidelines for Recombinant DNA Research. I am using recombinant DNA techniques to study immunoglobulin genes in the mouse. I have read the Proposed Revised Guidelines (Federal Register 43(146), 33042-33178), and find them more rational than the extant Guidelines. For example, they recognize that in many cases it is safer to work with viral DNAs in the form of recombinant DNA than as a virus particle or as viral DNA. I agree with your statements that the years of experience with recombinant DNA have shown that the likelihood of a dangerous organism being produced is extremely low; and that the burden of proof should be shifted to those who would claim the experiments are dangerous. It is also true that as we learn more about the genomes of eukaryotes, we are learning how difficult (impossible?) it would be for a prokaryote to translate a eukaryote gene.

We have already experienced a tremendous increase in the pace of research in molecular biology due to cloning techniques. These Proposed Guidelines will help greatly in this respect, especially in the field of virology. The Proposed Guidelines will make it easier to use recombinant DNA techniques, and therefore, will help research progress more rapidly. I believe this will have great benefits to humankind in the fields of health and agriculture.

I also believe that the NIH has done a commendable job of regulating recombinant DNA research. You have gathered together tremendous expertise in making your studies and decisions. I think it is reasonable for NIH to determine safety procedures for research because it has this expertise available to it. However, it is still very cumbersome to operate within these regulations because of the large bureaucracy involved. The Proposed Guidelines have done much to correct this by allowing us to apply to our local IBCs for the minor decisions. However, if Congress were to legislate the Guidelines, the bureaucracy would probably increase, and I expect changes in procedures would be even more difficult to implement. (Furthermore, Congress should have much more important things to do). If individual states were to legislate, the situation would be even worse, because it is very improbable that they would gather the necessary expertise.

However, I do have a criticism of the Proposed Guidelines. I believe they are too strict given the apparent lack of dangers in these experiments. For

MEMORIAL HOSPITAL FOR CANCER AND ALLIED DISEASES
SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
SLOAN-KETTERING DIVISION, GRADUATE SCHOOL OF MEDICAL SCIENCES, CORNELL UNIVERSITY

example, E. coli K-12 cannot infect and grow in humans or animals. There is no reason to believe this would differ for E. coli containing an eukaryote gene, even one that is functional in the bacteria. Therefore, I do not think it is necessary to use an EK2 host, e.g. X1776 (when using non-transmissable plasmids as vectors), for any of the experiments permitted in the Revised Guidelines. I hate to point to other research that has more potential danger, but I know there is such, and that such research is progressing safely without guidelines because the scientists are informed of the dangers involved and behave accordingly. Molecular biologists have been handling viruses and using radioisotopes for years. They know how to handle them without having to write MUAs. The NIH has helped them do so, I realize, and I do heartily approve of the NIH studying the dangers in biological research and of informing those involved. I think this is the most important contribution to laboratory safety you can make.

Thank you for your consideration and good luck in your efforts.

Sincerely yours,

Janet Stavnezer, PhD.
Associate, Sloan-Kettering Institute
Assistant Professor
Sloan-Kettering Division of Cornell
University
Graduate School of Medical Sciences

JS:cv

DEPARTMENT OF AGRICULTURE
OFFICE OF THE SECRETARY
WASHINGTON, D. C. 20250

SEP 28 1978

Donald S. Frederickson, M.D.
Director, National Institutes of Health
Department of Health, Education, and Welfare
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

This is a followup to my interim reply to your letter of August 3 requesting the response of the Department of Agriculture to the Proposed Revised Guidelines on Recombinant DNA research. It also replies to your letter of July 27 to Dr. Nielson, to which Dr. Bertrand provided an interim response, as well as to others sent to the Department with copies of the guidelines. The Department supports in principle the proposed guidelines as presented by NIH. You are to be complimented on the excellent presentation of background information and rationale for the revisions in your accompanying decision and environmental impact assessment statements.

The scope and containment levels for recombinant DNA research in relation to plants, nonprimate vertebrates and invertebrates, including pathogens and other microflora associated with these organisms, are much more in line with the perceived risk of using these organisms in recombinant DNA experiments than are these points in the current guidelines.

Agriculture is pleased to have contributed to revisions in these areas through the careful study of needs by respected scientists at the USDA-NSF sponsored Airlie House workshop on Recombinant DNA Research in Relation to Plant and Animal Sciences, and the USDA-NSF-NIH sponsored workshop on Risk Assessment of Agricultural Pathogens. The acceptance of most of the recommendations from the workshops by the RAC and their subsequent incorporation into the guidelines was extremely important to agriculture. This demonstrates the cooperation between agencies and scientists that must occur before the tremendous potential of recombinant DNA technology can be realized in the production and improvement of the food and fiber train in the United States. We trust this cooperation will continue as research provides scientific evidence to support future guideline revisions and updating.

The most important changes in the recent guideline revision include the reduction in physical containment levels from P3 or P4 for many experimental systems and the exemption of certain other systems from the guidelines. These changes allow safe, independent investigation by scientists in public and private institutions throughout the country without tremendous expenditures of limited research funds to construct high containment facilities. Review of research by a local Institutional Biosafety Committee (IBC) is endorsed, since this process places the initial review with the scientists having expertise not only in genetics and nucleic acid research but also in local laboratory facilities and practices. It also provides for input from non-science faculty and the local citizenry. Through our Science and Education Administration (Cooperative Research), USDA is assisting colleges and universities in establishing IBC's and identifying agricultural scientists who have been appointed to the Committees. We had already taken steps to assure that guidelines were followed for all USDA supported research, and will continue to do so under the revised guidelines.

A few points in the guidelines have been singled out for direct comment. Under Exemption I-E-4, experiments with certain bacterial genera known to exchange DNA with E. coli are exempt from the guidelines. However, the list of exchangers in Appendix A did not include Xanthomonas, a bacterial plant pathogen which the Risk Assessment Workshop considered to be an exchanger. We anticipate a need to add Xanthomonas to this list in the future and thus feel it would be beneficial to have a clarification of the criteria for gene exchange better defined in the guidelines.

The anticipated potential of recombinant DNA in agriculture will be difficult if not impossible to realize with the E. coli K-12 host-vector system. Therefore, it is imperative that attention be given to the development and approval of alternate HV-1 systems that may be useful in genetic engineering of plants and invertebrates.

The Department agrees with the need and purpose of prohibiting certain experiments at this time, but wishes to comment on two of the prohibited experiments in the revised guidelines as they have a direct bearing on agriculture. Plant pathogens are known to have a wide variability in virulence and host range that corresponds to the genetic diversity of their host plants. The ability to manipulate virulence by any means, including recombinant DNA, is important to the understanding of the biochemical and physiological basis for virulence. Since the precision that is possible with recombinant DNA may provide a powerful research tool, waiver of this prohibition to enable research on virulence to proceed should be considered by USDA and NIH for inclusion in this revision of the guidelines.

The prohibition of deliberate release of any organism containing recombinant DNA into the environment is, of course, of great concern to agriculture. The Department concurs with your decision to include this prohibition on the basis that evidence does not indicate benefits from such a release are near realization, but is pleased to see the waiver provision. It is hoped that research soon to proceed under the new guidelines will push us rapidly toward this goal. At that time, we will gladly accommodate your request that USDA be deeply involved in developing a process for determining the requirements for waiver of this prohibition and in seeing that the requirements are met.

Sincerely,

DAVID R. ULICER
Deputy Assistant Secretary

NATIONAL SCIENCE FOUNDATION
WASHINGTON, D.C. 20550

OFFICE OF THE DIRECTOR

September 28, 1978

Dr. Donald S. Fredrickson
Director, National Institutes of Health
Bethesda, Maryland 20014

Dear Don:

We support and concur in the substance of the proposed revised guidelines insofar as they relate to the conduct of experiments involving recombinant DNA. The proposed revised guidelines are clearly stated and make prudent use of available facts. They set standards that protect our health and environment from conjectural risks, while permitting research to proceed with adequate but unemcumbering caution.

We believe that proper separation has not been made between the National Institutes of Health's (NIH) responsibility for the development of the guidelines and the designation of certain aspects of their implementation and interpretation. This new tool of biological research will be used to enhance the mission of Federal agencies other than NIH, principally the Department of Agriculture (DOA), the Department of Energy (DOE), and the National Science Foundation (NSF). As long as safety is not compromised, and uniform standards are used each should pursue its goals expediently. By removing the flexibility in the current guidelines that allows other agencies to use discretionary powers, the proposed revised guidelines in effect subject the research of other agencies to the additional requirement for NIH approval procedures. This approaches establishing a regulatory role for NIH. Just as the proposed revised guidelines recognize that the responsibilities of the Institution Biosafety Committees (IBC) must be enhanced to make them partners in implementing the guidelines, so too, should the discretionary powers of other research agencies be recognized.

We believe each agency can exercise its independent responsibility without diminishing the central role of NIH in coordinating and communicating all decisions. Specifically, the Recombinant DNA Advisory Committee (RAC) should be recognized as a de facto national advisory body for all agencies. Accordingly, RAC recommendations could be considered directly by each agency. You pointed out in your Decision Document that, in addition to recommendations from RAC, you may seek additional advice for NIH purposes. In the same vein, we believe that other agencies should have this option. No agency should unilaterally act on a RAC recommendation; but within 30 days after each RAC meeting, representatives from

concerned agencies should meet to review the basis for accepting, rejecting, or postponing action on RAC recommendations. Consensus on acceptance of a RAC recommendation would be tacit approval or certification to be publicly announced by the Office of Recombinant DNA (ORDA). Similarly, the reasons for postponement of action or rejection of RAC recommendations should be announced by ORDA as soon as possible. This suggestion has three advantages over the approval and certification procedures of RAC recommendations described in the proposed revised guidelines: 1) Each agency can fulfill its own responsibilities while NIH coordinates the evolution of a single set of standards, criteria and principles for guiding recombinant DNA research in the U.S.; (2) Implementation of RAC recommendations will be accomplished in a timely and orderly manner; and (3) Scientific considerations will be clearly separated from other considerations. Specific matters that any agency wished RAC to consider can be directed to the committee via ORDA.

As you know, NSF accepts Sections I, II, and III of the current guidelines but has developed its own Section IV, substituting NSF roles and responsibilities for those of NIH. In the proposed revised guidelines, the roles and responsibilities ascribed to NIH are found in all of the sections in the documents under review. Presentation of the proposed guidelines in this manner does not permit other agencies to adopt the revisions for their purposes simply, and would inevitably lead to confusion when NSF-supported researchers and IBC's try to distinguish NSF and NIH requirements and procedures. We urge that every effort be made to avoid this confusion.

The NSF endorses the proposal to enhance IBC power by including approval of Memoranda of Understanding and Agreement (MUA) and lowering of containment in specified instances. Granting agencies will review IBC approval actions, but will not review decisions of disapproval or decisions of nonaction, i.e., postponements. Since it is possible that some committees may have misconceptions about some parts of the guidelines, researchers should have recourse to alternative decision processes. Accordingly, we recommend provision for the establishment of a formal appeals mechanism so that contested decisions may be presented to RAC for arbitration.

Other specific potential problem areas we wish to call to your attention are the following:

I-C General applicability - We support the principles of compliance with uniform national guidelines, but it is not clear by what authority these guidelines can be made applicable in certain institutions to recombinant DNA research not supported by Federal funds. Conversely is it intended to exclude federally supported research not carried out at or affiliated with such institutions such as small businesses?

III-A-3-b-(1) Characterized Clones - Is it intended that IBC's will notify ORDA of the approval of lower containment rather than the agency supporting the research? With regard to the exceptions, is it intended that prior NIH approval is required for projects supported by agencies other than NIH?

III-C Experiments with eukaryotic host vectors - What role in evaluating new case-by-case situations will the supporting agency play for research not supported by NIH?

IV-A-1-C Registration of research - Requiring institutions to register with NIH all projects approved by the IBC should be limited to NIH supported research and recombinant DNA research supported by non-federal sources. For Federally supported research other than NIH, each agency should maintain its own registry, which can be routinely added to the NIH registry. This will more effectively capture information about intramural research at national laboratories and experiment stations and will more accurately track proposed extramural research. IBC's approve MUA's when proposals are submitted to funding agencies. Final action on those proposals may not take place until 6-9 or more months later. At that time a project can be funded or disapproved. If funded, it is possible the recombinant DNA experiments may be specifically excluded from support. Reporting of these details by the cognizant agency is a more effective mechanism. With respect to registration it would be helpful if the term research "project" were defined. Can a single grant or MUA involve more than one project? If so, must each be registered separately?

I hope that the next version of the guidelines will accommodate NSF concerns expressed in this letter. Interagency cooperation and coordination and drawing proper boundaries between jurisdictional authority has been effective in the past. This should continue in order to avoid confusion within the scientific community and to accomplish our common goal of enhanced research, minimum delay and appropriate precautions for safety. In closing, you and your staff should receive strong praise for the responsible and effective development of national standards for the conduct of research using recombinant DNA techniques.

Sincerely yours,

Richard Atkinson

Richard C. Atkinson
Director

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Executive Director

September 28, 1978

Mr. Peter Libassi
General Counsel
H.E.W.
200 Independence Avenue SW
Washington, D. C.

Dear Mr. Libassi:

Enclosed herewith are comments on the proposed revised Guidelines for recombinant DNA research (July 28, 1978) submitted to the National Institutes of Health Director Donald Fredrickson by our organization.

The three sections of our comments are divided as follows:

Part I - Structures and Procedures
Part II - Technical Analysis and Comments
Part III - Protection of Employees

We strongly urged Dr. Fredrickson that great consideration be given to the following:

1. that proposed technical revisions <u>await experimental data to justify weakening any standards;</u>

2. that the Recombinant DNA Advisory Committee be expanded <u>to comply with the Federal Advisory Committee Act</u> which requires a "balance of views".

That the September 15, 1978 hearing was sponsored and chaired by officials of HEW, rather than by those of NIH whose function it is to promote and fund recombinant DNA research, was an aid to a more objective approach. We trust that the review of comments by HEW officials, such as yourself, will expand that objective approach to embrace caution and care in those amounts necessary to protect the public health against the potential hazards of this new, untried technology.

Please do not hesitate to call upon us for any help that we may provide.

Yours very truly,

Francine Robinson Simring
Francine Robinson Simring
Executive Director

cc: Kennedy, Stevenson
Ottinger, Rogers

FRS:fh

[Part I printed on page A-175.]

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TECHNICAL ANALYSIS AND COMMENTS

ON PROPOSED REVISED GUIDELINES FOR RECOMBINANT DNA RESEARCH

FEDERAL REGISTER, JULY 28, 1978
PART IV

INTRODUCTION

This section of comments on proposed revisions concerning the technical aspects of recombinant DNA experimentation is the second of a three-part report submitted by the Coalition for Responsible Genetic Research.

Part I - Structures and Procedures
Part II- Technical Analysis and Comments
Part III-Protection of Employees

A. *"Exchangers"*

The proposed revised guidelines contain a list of prokaryotes which are purported to be "exchangers"; i.e. they can either be shown to exchange chromosomal DNA in the laboratory, or their DNA homology is 20% or greater (pp. 33089, 33158). Recombinant DNA from any organism on the list would be permitted to be propagated in any other organism on the list. This kind of work would be exempt from the Guidelines.

1. Most of the organisms are listed by genus, when the available evidence only addresses possible exchanges between particular species of any of the genera. The extent of interspecies exchange within the genus Pseudomonas has not even been well-characterized. Only organisms designated by species can

legitimately be considered part of an "exchangers" list, and then only where more detailed information is available (see below).

2. Natural rates of exchange have not been taken into account in arriving at the list of "exchangers". The demonstration of any degree of chromosomal DNA exchange is sufficient for membership on the list. Thus, while only prokaryotes are on the present list, the consistent application of this principle could ultimately place eukaryotes and prokaryotes on the same "exchangers" list (that is, exempt from the Guidelines) since some limited exchange has undoubtedly occurred between certain pairs (i.e. Agrobacterium tumefaciens and its host plant).

3. The rationale for membership on the "exchangers" list completely ignores ecological considerations. For example, recombination experiments between wild type strains of E. coli (those strains which inhabit the normal human large intestine) and Salmonella (some species of which are responsible for severe food poisoning) are proposed to be exempt from the Guidelines, presumably because some species of these genera can exchange chromosomal DNA in the laboratory. There is no discussion of whether these microorganisms ever occupy the same ecological niche, and thus have the opportunity to exchange in nature. Fredrickson, in his statement, talks about the lack of success in converting E. coli K12 into a pathogen by insertion of Salmonella genes (p. 33059). Has this been attempted with wild type E. coli? Under the proposed revised Guidelines, such an experiment, with a host with none of the inherent weaknesses of K12, could be performed subject to no regulations.

RECOMMENDATIONS: Members of the "exchangers" list should be designated only by species name, and only where exchange can be demonstrated in a realistic ecological setting at a non-vanishing rate. Furthermore, recombination between members of the list should be subject to P2 physical containment and thus remain within the Guidelines.

B. *Cloning of Animal Cell Transforming Viruses*

The proposed revised Guidelines accept the recommendations of the "Ascot Conference" and have lowered containment levels for the cloning of animal cell transforming viruses (such as polyoma and SV 40)(p.33077). This decision does not take into account the results of the Rowe-Martin risk assessment experiment with polyoma, preliminary results of which were reported at the 1977 Falmouth Conference, but were not included in the published proceedings of the conference (Journal of Infectious Diseases, April 1978).

The most recent summary of these experiments were reported by Wallace Rowe at the Recombinant DNA Advisory Committee meeting of August 1-3, 1978. Briefly, it has been shown that polyoma DNA itself, de-proteinized, without a capsid(virus coat) can cause infection when injected into the bloodstream or or fed into the colon of a mouse. Roy Curtiss, in a letter to Fredrickson dated April 12, 1977 stated that he believed that such experiments would not give positive results. This unexpected result of the risk assessment experiment has received no publicity apart from informal statements by the investigators.

The significance of the experiment lies in its demonstration that polyoma DNA itself is an etiologic agent. Incorporated into a plasmid it is not infective, but if the plasmid is cleaved by a nuclease (which are ubiquitous) it is rendered infective. Thus one of the scenarios envisaged by critics of recombinant DNA research, i.e. that a disease-causing agent might be carried to new ecological niches by such experimentation, is now close to realization. All that is required for such a result is the lowering of physical and biological containment for these experiments. Polyoma DNA in a capsid can thrive only in intra-cellular environments; polyoma DNA in bacteria can thrive (and be

infective) in intestines.

RECOMMENDATION: Experiments involving mammalian transforming viruses should be performed at P4-EK2 containment levels.

C. *Shotgun Cloning of DNA* (p. 33077)

The proposed revised Guidelines distinguish between shotgun cloning of DNA from organisms which are known to produce potent polypeptide toxins and those which do not. Since many "normal" substances produced by any vertebrate (hormones, neuro-transmitters, cell recognition factors) would be highly toxic if presented at the wrong time or place to another animal, this distinction is meaningless.

RECOMMENDATION: All vertebrate shotgun experiments should be considered to involve producers of polypeptide toxins, and thus be performed under P3-EK2 containment.

D. *"Flexibility"*

The proposed revisions have a provision for "flexibility" that would allow, for example, experiments designated at the P3-EK1 level to be performed at the P2-EK2 level (pp. 33074, 33113). Since distinctions between the various P levels, up to P3, are very dependent in practice on training and diligence of personnel, it would seem that the validity of the trade-off would vary from laboratory to laboratory. Up to P3 it would seem that biological containment would be most reliable, but trade-offs in certain cases would probably be reasonable.

However, P4 represents the closest situation we have to absolute containment. For experiments designated at this level to be done at P3 containment would represent a serious falling away from the most stringent conditions which have been reserved for those experiments generally acknowledged to be in the highest risk category.

RECOMMENDATION: No other physical containment level should be substituted for the P4 designation without in-depth study by the RAC and the NIH Director of the specific experiment proposed.

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COMMENTS ON PROPOSED REVISED GUIDELINES FOR

RECOMBINANT DNA RESEARCH
FEDERAL REGISTER, JULY 28, 1978
PART IV

INTRODUCTION

This section of comments on the proposed revised Guidelines concerning protection of the health of the potentially exposed worker is the third of a three-part report submitted by the Coalition for Responsible Genetic Research.

Part I - Structures and Procedures
Part II - Technical Analysis and Comments
Part III- Protection of Employees

The following comments indicate areas of inadequacy, recommend improvements and changes, and also touch on the mechanism for policy change:

I. *Industrial Regulation*

The Guidelines provide only for voluntary compliance by industry with its standards and procedures. "...provision is now made for the private sector to register voluntarily its recombinant DNA activities with the NIH." (p. 33045) Because of the voluntary nature of the directive, industry will not be subject to sanctions for non-compliance. This is especially of concern because volume-oriented production sharply increases the probabilities of biologic mishap and worker exposure.

II. *Environmental Monitoring*

The proposed revised Guidelines provide no stipulations for environmental monitoring for recombinant DNA materials. Indeed, a mechanism for monitoring for presence in the air does not yet exist for much of recombinant DNA material.

III. *Biological Monitoring and Medical Surveillance*

The Guidelines are inadequate in their specifications for biologic monitoring and medical surveillance. The institution would be given responsibility for the determination "in connection with each project, the necessity for medical surveillance of recombinant DNA research personnel..." (p. 33084 IV-A-1-e). Such a program "might include, for example, records of agents handled, active investigation of relevant illnesses acquired by recombinant DNA research personnel and the maintenance of serial serum samples". Such wording offers the institution the option of determining that there is no need for medical surveillance.

The lack of specificity of the Guidelines' language in this area of protection of employees may well exclude some worker populations. Stipulations for "research personnel" does not provide for members of the custodial, maintenance and janitorial staffs. Often these latter groups are at special risk because of their lack of knowledge of their conditions of exposure. Further, if each institution is given responsibility for each project under its aegis, the variability in program development and implementation among diverse institutions would provide for the exposed worker unequal protection under the law.

IV. *Worker Education*

Guideline requirements for educating workers about the potential hazards of working with recombinant DNA materials are inadequate and vague. While it is stated that the NIH has a contract with the American Society for Microbiology

to develop "minimum standards for training participants in recombinant DNA research " (p. 33053), once again other worker populations such as custodial, maintenance, and janitorial employees are overlooked. This lack of attention to the needs of non-research personnel for education is also illustrated in the directive to the principal investigator who shall "make available to the laboratory staff copies of the approved protocols that describe the potential biohazards and the precautions to be taken." (p. 33085 IV-A-4-m-[1])

The vagueness of some terminology can lead to ineffectiveness of collected data. For example, experience with industrial Material Safety Data Sheets, which in theory indicate the biohazards of exposure, reveals that it is necessary to require that these "protocols" specify both acute and chronic effects; not only those known with certainty but also those strongly suspected.

V. *Emergency Spills*

The Guidelines do not adequately treat the courses of action in the event of emergency spills. It is mandated that the Biological Safety Officer shall develop "emergency plans for dealing with accidental spills and personnel contamination..." (p.33085 IV-A-3-b). Also that the Institutional Biohazard Committee shall "review and approve emergency plans covering accidental spills..." (p. 33085 IV-A-2-d). Such directives permit utilization of varying levels of expertise among members of the IBC, et al. Only specific and detailed instructions in the Guidelines for emergency spills can overcome the problems of uneven expertise and institutional pressures.

VI. Institutional Biohazard Committee

The Guidelines omit representation of workers in their specifications for the constituency of the IBC. In addition, representation of experts trained in the fields of worker and public health is inadequate.

"The IBC shall be a committee...that has the experience and expertise to assess the safety of proposed recombinant DNA research projects...Its membership should include...disciplines relevant to recombinant DNA technology, biological safety and engineering. It is recommended that the IBC also include members knowledgeable about such matters as applicable law, standards of professional conduct and ractice, community attitudes, and the environment. It is recommended that at least one member be a non-doctoral person from a laboratory technical staff." (p. 33085 IV-A-2)

The use of the word "recommend" rather than "directed" or "mandated" or "required" permits the IBC's free rein to constitute their roster as they may desire. Further, the need for experts in epidemiology, virology, public health, industrial hygiene, infectious disease, etc. is not addressed.

VII. *Sanctions and Compliance*

The language employed in the area of sanctions and compliance is too weak to ensure compliance. "All NIH-funded projects involving recombinant DNA technology must comply with the NIH guidelines. Non-compliance may result in suspension, limitation or termination of financial assistance for such projects and for other recombinant DNA research at the institution."

VIII. *Mechanism for Policy Change*

Changes in policy are vested in the Director of the NIH. Unchecked, extensive powers governing recombinant DNA research which come under his purview include:

- the power to revise and amend the Guidelines (p.33086 IV-B-1b)
- the power to certify new host-vector systems (p.33086 IV-B-1c)
- the power to permit exemptions from experimental prohibitions (p.33086 IV-B-1e)

A sharing of these powers would help to ensure broader perspectives in crucial decision-making for the technology.

RECOMMENDATIONS: The following changes and additions to the proposed revised Guidelines will increase protection of the health of the worker and the public.

I. *Industrial Regulation*

The NIH Guidelines should be extended to include industry on a mandated basis.

II. *Environmental Monitoring*

Existing mechanisms for environmental monitoring should be required, and programs to develop necessary mechanisms be instituted.

III. *Biological Monitoring and Medical Surveillance*

1. All laboratories conducting recombinant DNA research should be required to keep official OSHA health and safety log forms.

2. National standards for medical surveillance programs specific for each class of organisms and group of experiments should be developed and promulgated, in consultation with the Advisory Committee (to be reconstituted as described below).

3. Medical surveillance should be required for all workers potentially exposed to recombinant DNA material, and when appropriate, their families.

4. Ongoing epidemiologic and bio-statistical analysis of the morbidity data should be required as it is accumulated at this central registry. In this manner, trends can be detected early on.

IV. *Worker Education*

The guidelines should specify clearly the required components of training and of biohazard education. Further, they should delineateboth acute and chronic, known and suspected effects of exposure to the specific host-vector system involved. This educational program must be made available to all potentially exposed workers.

V. Emergency Spills

A set of national standards should be provided for in the Guidelines for the handling of emergency spills. These standards should be drawn up by the reconstituted Advisory Committee to the Director, NIH.

VI. Institutional Biohazard Committee

The Guidelines should mandate that the membership include at least two non-doctoral laboratory staff persons and at least two members from the custodial and janitorial sectors. Membership should also include at least one physician trained in(clinical and research)infectious diseases, at least one epidemiologist and at least one environmental scientist. None of these may be affiliated with the institution involved.

VII. Sanctions and Compliance

In reference to the stipulation "Non-compliance may result in suspension..." (p. 33087 IV-D-1a), the word "may" should be stricken from the sentence and the word "shall" be substituted. Fines appropriate to the nature of violations should be levied in addition to the cessation of funding. In addition to the foregoing, criminal penalties should be levied for certain willful violations of the Guidelines.

VIII. Mechanism for Policy Change

The Recombinant DNA Advisory Committee to the Director of NIH should be reconstituted by Guidelines mandate to include representatives from OSHA, EPA, appropriate labor unions, at least one physician trained in(clinical and research)infectious diseases, at least one epidemiologist, at least one environmental scientist, and at least one medical microbiologist.

Only after consultation with and approval by the reconstituted Recombinant DNA Advisory Committee may the Director use his powers to revise and amend the Guidelines; to certify new host-vector systems; and to permit exemptions from experimentation prohibitions.

DEPARTMENT OF TRANSPORTATION
RESEARCH AND SPECIAL PROGRAMS ADMINISTRATION
WASHINGTON, D.C. 20590

SEP 29 1978

REFER TO:

Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Sir:

The following are comments on the July 28, 1978, publication of the NIH proposed revised guidelines of recombinant DNA research. The comments deal only with the transportation impacts of the revised guidelines.

1. The revised guidelines address transportation at Section II-C, and also the supplemental "Laboratory Safety Monograph". The revised guidelines would be the operative document from an enforcement standpoint, while the Monograph is merely illustrative of the requirements to be established in the guidelines. As a practical matter, the Monograph now makes fairly clear what is intended in the revised guidelines, but we believe the guidelines should be so drafted as to leave no question on intent or enforceability. Since present DOT requirements do not apply to recombinant DNA materials, the guidelines must stand on their own until DOT is able to propose and implement transportation rules in support of NIH. Due to the possibility that the revised guidelines may attain the status of law by legislation, we think it prudent to consider enforcement in the drafting.

2. It is possible to understand II-C of the revised guidelines to mean that adherence to packaging requirements in 42 CFR 72.25 is necessary only if the host or vector organism is a listed etiologic agent. The language of II-C should expressly subject shipments of RDNA containing organisms and viruses to the specified requirements of 42 CFR 72.25, since one could "comply" with that section under the present II-C draft by shipping an RDNA containing organism that is not listed in 42 CFR 72.25(c).

3. If a separate set of restrictions are to be used for RDNA molecules, not contained in an organism, that point should also be established in the text of II-C. In Section V.D. of the Monograph, shipment of RDNA molecules is to be subject only to very limited packaging restrictions which are essentially paraphrased from 42 CFR 72.25(b), but not mentioned in the text of II-C.

4. Reference in the revised guidelines to tariff C.A.B. No. 82 is, in our opinion, unnecessary. The tariff merely describes the conditions

under which carriers will accept shipments and is more properly viewed as binding the carrier rather than the shipper. Moreover, tariff provisions sometimes vary from regulatory requirements. The references to tariff restrictions in the Monograph should be adequate.

5. In view of the above, we would suggest the following text for II-C of the revised guidelines:

II-C. Shipment. Recombinant DNA molecules may be shipped only as an etiologic agent under requirements of the U.S. Public Health Service and the U.S. Department of Transportation (Section 72.25, Part 72, Title 42, and Sections 173.386-.388, Part 173, Title 49, U. S. Code of Federal Regulations) as specified below:

II-C-1. Recombinant DNA molecules, contained in an organism or virus, when offered for transportation or transported, are subject to all requirements of Section 72.25(c)(1)-(5), Part 72, Title 42 CFR, and Sections 173.6 387-.388, Part 173, Title 49 CFR.

II-C-2. Recombinant DNA molecules, contained in an organism or virus which is a viable host or vector organism requiring P4 physical containment, when offered for transportation or transported, are also subject to Section 72.25(c)(6), Part 72, Title 42 CFR.

II-C-3. Other recombinant DNA molecules, when offered for transportation or transported, are subject to all requirements of Section 72.25(c)(6), Part 72, Title 42 CFR.

II-C-4. Additional information on packaging and shipment is given in "Laboratory Safety Monograph - A supplement to the NIH Guidelines for Recombinant DNA Research."

Sincerely,

Douglas Crockett

Douglas Crockett
Chief, Standards Division
Office of Hazardous Materials
Regulation
Materials Transportation Bureau

MEMORIAL SLOAN-KETTERING CANCER CENTER

NEW YORK, NEW YORK 10021 TRAFALGAR 9-3000

TOWARD THE CONQUEST OF CANCER

Office of the President

September 29, 1978

Peter Libassi
General Counsel
Dept. of Health, Education & Welfare
Washington, DC

Dear Mr. Libassi:

I have been told that the Friends of the Earth are pressing their case against modification of the NIH guidelines for Recombinant DNA research. I am in flat disagreement on straightforward scientific grounds, with the rigid position taken by their organization.

I write to you at this time because my name has appeared in various Friends of the Earth literature as a member of their Advisory Council. I resigned from this Council on December 14, 1977, because of the civil action suit against HEW then proposed by the organization. A copy of my letter to Mr. David H. Brower at that time is enclosed herewith.

Sincerely,

Lewis Thomas, M.D.

enc.

[A-410]

MEMORIAL HOSPITAL FOR CANCER AND ALLIED DISEASES
SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
SLOAN-KETTERING DIVISION, GRADUATE SCHOOL OF MEDICAL SCIENCES, CORNELL UNIVERSITY

December 14, 1977

David R. Brower, President
Friends of the Earth
72 Jane Street
New York, New York 10014

Dear Mr. Brower:

For some time, my name has been associated with Friends of the Earth as a member of the Advisory Council. Although I've had no special duties to perform I have valued this connection and have generally supported the objectives of the organization.

Now, to my regret, I find myself in disagreement on an issue which is of major importance for the future of biomedical science: recombinant DNA research. As a long time student of infectious disease and microbial pathogenicity, I regard the claims that this technology represents a new and major hazard to health as fanciful, grounded in ignorance of the subject, and too often based on ideological rather than scientific opinion. I believe that the NIH guidelines provide more than adequate assurance of safety if there were a hazard.

I have just seen a copy of the civil action file in the suit against H.E.W. and N.I.H. on this issue, obviously intended to put a stop to all recombinant DNA research, with or without NIH guidelines. I do not agree at all with the assertions on which this case is constructed, and I belive that the net result of the action, if successful, will be damage to the whole scientific enterprise in this country.

Therefore, with regret, I must tender my resignation from the Advisory Council of Friends of the Earth.

Sincerely,

Lewis Thomas, M.D.

[A-411]

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 3 1978

OFFICE OF
RESEARCH AND DEVELOPMENT

Joseph G. Perpich, M.D., J.D.
Associate Director for
Program Planning and Evaluation
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Perpich:

I am writing you in regard to your note of ~~September 7, 1978~~ August 7, 1978, to Dr. Barth concerning The Proposed Guidelines to control Recombinant DNA research funded by the National Institutes of Health. Dr. Barth has recently accepted an Intergovernmental Personnal Act position with the University of Nevada at Las Vegas and I am acting in his former position as Deputy Assistant Administrator for Health and Ecological Effects.

I realize that comments at this time are too late to be coordinated for the public hearing and I apologize for this lateness.

My staff has reviewed the Proposed Guidelines and in essence feel that they are adequate. There were a number of items of which the most significant relates to the brevity of the coverage of the effects on water, air, plants, insects, fresh water and marine organisms.

I feel that due to the lateness of our comments, we should await your publication of those you have already received and at that time see whether or not our concerns have been addressed.

We are looking forward to receiving further information as it develops.

Sincerely yours,

Thomas A. Murphy
Acting Deputy Assistant Administrator
for Health and Ecological Effects

[A-412]

UNIVERSITY OF CALIFORNIA, BERKELEY

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SCHOOL OF PUBLIC HEALTH

NAVAL BIOSCIENCES LABORATORY
NAVAL SUPPLY CENTER
OAKLAND, CALIFORNIA 94625

October 3, 1978

Dr. Donald S. Fredrickson, Director
Department of Health, Education,
and Welfare
Public Health Service
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

I have just received the July 1978 "A Supplement to the NIH Guidelines for Recombinant DNA Research" which is entitled Laboratory Safety Monograph.

This monograph is an excellent piece of work which should redound much to the credit of its authors. It has added clarity and logic to many of the physical and biological safety procedures described briefly in the guidelines. The monograph can stand alone as a substantial contribution in the field of microbiology laboratory safety.

I am aware that the monograph was prepared by the Office Research Safety. As a person often critical of such public documents, I should like to say "well done". The monograph yields strong indication that the safety aspects of the recombinant DNA guidelines program is in good hands.

Sincerely yours,

Mark A. Chatigny
Assistant Director

MAC:lf

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MALCOLM M. B. STERRETT, MINORITY STAFF DIRECTOR

United States Senate
COMMITTEE ON COMMERCE, SCIENCE
AND TRANSPORTATION
WASHINGTON, D.C. 20510

October 13, 1978

The Honorable Joseph A. Califano
Secretary
Department of Health, Education
and Welfare
Washington, D.C. 20201

Dear Mr. Secretary:

I have received your reply of September 12 to the June 1 inquiry of several Senators regarding the use of existing statutory authorities, especially Section 361 of the Public Health Service Act, to regulate recombinant DNA research. I am writing to support your call for new legislation and to recommend several changes in the proposed revised NIH guidelines.

As you know, the Senate Subcommittee on Science, Technology and Space recently issued an oversight report, "Recombinant DNA Research and Its Applications," in which the majority observed that, in view of the nature of the concerns about recombinant DNA techniques and the history of Section 361, the absence of evidence that the products of the research can cause human disease is not a conclusive argument against the use of that authority. Neither your reply nor the March 1977 report of the Federal Interagency Committee on which you rely addresses these points. Nevertheless, I respect your desire for a specific legislative mandate and accept your decision not to invoke Section 361 except in the unlikely event of a demonstrated health emergency.

I find more puzzling your observation that the Food and Drug Administration does not have authority to impose any requirements on recombinant DNA research since it has not yielded any products subject to FDA regulation. In your letter to me of February 27, 1978, you stated that FDA ". . could, under existing authority, require any firm seeking approval of a product which may be the end product of recombinant DNA research to certify to the Agency that it has complied with the NIH guidelines on recombinant DNA." While FDA may not be able to monitor research in progress, such regulations as you described in your earlier letter would at least put firms on notice that noncompliance with the guidelines would be grounds for the agency's withholding approval of a product of that research. The recent successful

laboratory production of human insulin by recombinant DNA techniques, although far from commercialization, suggests that the time is appropriate to issue these regulations, as do the comments of Eli Lilly Company to Dr. Fredrickson on the proposed revised guidelines. Lilly states, "Recombinant DNA technology is progressing rapidly from a laboratory phenomenon to developmental activities. The necessity for conducting scale-up experiments (greater than 10-liter volumes) is imminent."

The fact remains, however, that FDA action will not suffice to put all recombinant DNA research on the same regulatory footing. The provision of the proposed revised guidelines which would extend their coverage to privately supported research in institutions receiving NIH funds for RDNA work is a significant step in that direction, although, as I suggest in my comments on the revisions, it should be broadened to include all recombinant DNA research at institutions receiving <u>any</u> NIH funds.

Presumably, this extension of the guidelines' coverage will encompass some but not all of the research supported by Federal agencies other than NIH. You state in your letter that the Interagency Committee has "served to ensure a commonality of standards" among Federal agencies sponsoring recombinant DNA research, but it is my understanding that the Committee has not met in nearly a year. The <u>Federal Register</u> documents relating to the proposed revised NIH guidelines contain no indication that such agencies as the Departments of Energy and Agriculture, the Veterans Administration, and the National Science Foundation are prepared to adopt the revisions and require compliance with them. A survey of these agencies by the Subcommittee indicated that their procedures for monitoring compliance with the 1976 guidelines vary enormously; some have procedures comparable to those of NIH while others rely on informal assurances by investigators. In the case of the Department of Energy, responsible agency officials were not even aware when I wrote in March of recombinant DNA projects that were under way in a national laboratory under the Department's jurisdiction. Before the final revised guidelines are issued, I urge you to obtain the agreement of these agencies to follow the review procedures for NIH grantees, including requiring submission of the appropriate information to the Office of Recombinant DNA Activities.

The proposed voluntary registration system is a useful but limited addition to the guidelines. It will facilitate consultation between NIH and private sponsors of research, but apparently it does not resolve their concerns about the disclosure of proprietary information. Indeed, Section IV-C-4 of the revisions encourages private firms to "consider applying for a patent before

submitting information to DHEW." The willingness of companies to register even completed research projects may depend on further judicial or legislative clarification of the patentability of RDNA products. In general, I do not believe that the proposal invalidates the conclusion of the Subcommittee's report that "a program of voluntary compliance by and monitoring of industrial research activities is insufficient."

Primarily, for this reason, I am pleased that the Department continues to support "moderate" legislation. It is unfortunate that many in Congress drew the opposite inference from your delay in responding to our request for a prompt reply to our inquiry concerning Section 361 of the Public Health Service Act. Although some differences remain, it seems to me that there is general agreement on most of the elements of legislation enumerated in your letter. The Subcommittee's report endorses provisions clarifying the authority of the Secretary, facilitating the issuance of administrative regulations, and permitting exemptions for activities that pose no significant risk; and it advances a reasonable compromise on the issue of Federal preemption. I hope that we will have your support in passing such legislation early in the next session.

Let me explain why I believe that legislation is still advisable. It is true and, indeed, encouraging that the original concerns about possible health and environmental hazards associated with recombinant DNA techniques have diminished. This is primarily the result of recent scientific investigation and discussions among a wider range of biological and health scientists rather than failure to observe any case of illness or other harm. The latter merely tends to support the consensus that permitted activities conducted on the whole under prescribed physical and biological containment standards do not pose a significant risk. Be that as it may, the cautious approach that has been taken to the use of this technology is reasonable and it will continue whether or not legislation is passed. As Dr. Fredrickson observed in his introduction to the revised guidelines:

> ... It is not the time to conclude that (the guidelines) are being altered in preparation for their early abandonment. Understanding of gene regulation and expression is increasing inexorably and at an awesome pace. We may predict that ways will be found to achieve and control the translation of foreign genes by a variety of hosts.... In some proportion to the harvest of positive results, a capability must be maintained for observing any capacity of these experiments to yield harmful products....

With adequate training of investigators and laboratory personnel, physical containment procedures may become routine practice, and other requirements of the guidelines may be dispensed with on the basis of new evidence; but

some degree of Federal regulation will be necessary for the foreseeable future. I refer, for example, to the certification and monitoring of the use of host-vector systems. NIH anticipates applications for a variety of organisms other than E. coli K-12 and concedes that knowledge of their characteristics is inferior to the information acquired over many years about E. coli. It may be necessary to devise entirely new criteria in order to evaluate the safety of these new systems. Yet Dr. Fredrickson assures us that "the same considerations of safety and risk associated with the use of E. coli K-12 will also apply to any new host-vector system to be certified in the future." Subject to unusual case-by-case exceptions, moreover, the proposed guidelines retain the existing prohibitions on certain presumably hazardous categories of experiments, the release into the environment of organisms containing recombinant DNA, and the production of certain large cultures. In spite of suggestions that the burden of proof has shifted to those who would restrict the research, the revised guidelines are on the whole consistent with the present policy of imposing safeguards unless there is strong evidence that the activities pose no significant risk. As the Subcommittee's report points out, such evidence will be acquired gradually, over the course of several years.

In these circumstances, it is no less anomalous now than it was a year to two ago to restrict one class of researchers but not another, merely on the basis of their location and source of funds. Furthermore, voluntary adherence to the guidelines' prescriptions will become increasingly problematic as the research proliferates, more positive results are achieved, and the line between research and development is crossed. Far from obviating the need for any regulation, the progress that is being made in recombinant DNA research underscores the importance of universal standards uniformly applied.

The adoption of new NIH guidelines representing a more informed assessment of risks should facilitate action on legislation. My impression is that overall the proposed revisions represent a considerable advance in comprehensiveness and specificity over the present guidelines and that they will permit further progress in recombinant DNA research under appropriate safeguards. I commend Dr. Fredrickson, his colleagues and advisers for their efforts.

On the other hand, the proposed guidelines retain or create some ambiguities and weaknesses, particularly with respect to administrative procedures, that should be corrected. Fearful of "the heavy tax of formalism," Dr. Fredrickson has endeavored to retain as much discretion as possible in administering these regulations. Flexibility is important in a rapidly changing field of research, but the revisions reflect too little regard for accountability and predictability. I believe that the changes recommended in the attachment will further reduce public controversy and uncertainty among scientists and research institutions as well as promote compliance with the guidelines or with formal regulations if Congress acts next year.

Once your review committee has had an opportunity to examine these recommendations, I urge them to discuss any questions they may have with John Stewart and Steve Merrill of the Subcommittee staff.

Sincerely,

ADLAI E. STEVENSON, Chairman
Subcommittee on Science, Technology
and Space

Attachment

COMMENTS OF SENATOR ADLAI E. STEVENSON
ON THE PROPOSED REVISED GUIDELINES FOR RECOMBINANT DNA RESEARCH

1) Applicability

The proposed guidelines would apply to "all recombinant DNA research within the United States or its territories conducted at or sponsored by an institution that receives any support for recombinant DNA research from NIH." This provision does not make maximum use of NIH's authority to condition the receipt of Federal monies and could create administrative difficulties. I suggest that the guidelines be extended to all recombinant DNA research conducted at or sponsored by an institution receiving any NIH funds, regardless of whether they are earmarked for recombinant DNA research.

Dr. Fredrickson precisely states the rationale for this recommendation in the "Decision of the Director":

> The existence of guidelines for recombinant DNA research assumes their general application. Partial adherence within an institution would defeat the purpose of extending maximum protection to the community. Thus, it would be inconsistent for NIH to provide funds for biomedical research activities to an institution that did not meet the standards of the guidelines in all of its recombinant DNA research, regardless of the source of funding. (Emphasis added.)

According to an opinion of the American Law Division of the Congressional Research Service, it is highly unlikely that a court would overturn the broader condition, even on First Amendment grounds, so long as private funding is available for recombinant DNA experimentation and the application of the guidelines is relevant to the "overall objectives" of NIH funding.

Furthermore, it would be much simpler to identify institutional recipients of NIH funds than to decide whether the guidelines should apply to an institution in which recombinant DNA activities, although not expressly supported by NIH, nonetheless benefit indirectly from NIH money used, for example, to purchase equipment or to pay the salaries of researchers or technicians.

2) Exceptions

For the first time, the proposed guidelines would permit case-by-case exceptions to the existing prohibitions on certain categories of experiments, the release of recombinant DNA organisms into the environment, and the production of certain cultures in excess of ten liters. As Dr. Fredrickson correctly notes, "the widespread support for this authority reflects the realization that many important risk-assessment experiments may not be able to proceed otherwise." The House bill, H.R. 11192, endorses this principle as does the oversight report of the Senate Subcommittee on Science, Technology and Space. The grounds for such exceptions, however, go beyond the need for data to assess the hazards of recombinant DNA research. The "Decision" document states that exceptions may be made for experiments for which there are "compelling social or scientific reasons, for example, risk assessment experiments." The guidelines merely state that weight will be given in the decisionmaking "both to scientific and social benefits and to potential risks."

It is, of course, the responsibility of NIH to judge the scientific merit and social value of research proposals submitted for grants or contracts. No one questions the legality or propriety of conditioning the receipt of Federal money upon agreement not to engage in certain activities that may be dangerous. So long as all possible precautions are taken, it is also reasonable to waive a prohibition if that is necessary to determine whether the judgments on which it is based are correct. But it is quite another matter to make an individual exception to a general prohibition for a researcher who manages to persuade the Recombinant DNA Advisory Committee and the Director of the surpassing importance of his or her work while perhaps refusing another researcher who fails to present as good a case.

I question whether NIH officials have thought through the implications of this provision. I suggest that exceptions be made solely on the basis of need for risk assessment until there is sufficient evidence to justify removing an activity from the proscribed list. At the very least, the standard by which applications for exceptions will be judged should be clarified and the procedures for considering such applications should be elaborated. NIH should immediately address the conditions under which exceptions to the ten liter limit should be granted. Judgments about the social benefits of research should not be left to the Recombinant DNA Advisory Committee, a largely technical group.

3) Revisions of the Guidelines

Much of the criticism of the guidelines has concerned NIH procedures for revising them. Time and again critics have charged that the Recombinant DNA Advisory Committee and the Director have relied on the opinions of a selected group of scientists rather than on experimental data in recommending the relaxation of containment standards, that important data and judgments have not been published in time to permit broad scientific peer review, that standards for decisions on containment requirements are vague, and that NIH has been reluctant to give the public opportunity to review and comment on proposed changes.

I believe that it is time to lay these criticisms to rest by clarifying the standards and specifying the procedures for changes in the guidelines. Otherwise, doubts will remain that the guidelines provide adequate protection of public health and the environment. This is particularly important if, as the Federal Register documents imply, future revisions will be largely on a case-by-case basis, that is, by exempting specific categories of experiments from any regulation, by reclassifying experiments on the basis of new evidence, and by assigning containment levels to entirely new experiments.

In each of these cases, the criteria for recommendations by the RAC and decisions by the Director should be consistent, clear, and where possible precisely stated. For example, exemptions should be made only on the grounds that the experiments pose no significant risks or at least no

significant increase in risk over that present in nature. Criteria should be specified in detail. The meaning of "DNA exchange by known physiological processes," a category of exemptions, should also be defined. Serious consideration should be given to listing exchangers by species rather than genus.

The commitment simply to give "appropriate notice and opportunity for public comment" perpetuates the present uncertainties with regard to NIH procedures. The guidelines should provide for advance notice in the Federal Register of proposals for exemptions, classifications, and reclassifications. All material relating to the proposal should be available to the public. A public comment period should be specified, and notice of the agency's action should also be published in the Federal Register. These recommendations regarding procedures and criteria apply with equal force to the certification of host-vector systems.

4) Compliance

The new guidelines would delegate greater but not altogether clear responsibility for approval of recombinant DNA projects and changes in those projects to institutional biosafety committees. The General Applicability section implies that any research project approved by the institutional committee may be initiated without prior NIH approval. Elsewhere, it is indicated that prior NIH approval is required except for

initiation of non-NIH funded projects below the P4 level, changes in any ongoing projects below the P4 level, and single-step reductions in containment levels for experiments with purified DNA and characterized clones.

The Federal Register documents cite two reasons for this significant change -- bureaucratic delays in NIH review of new projects and proposed changes in ongoing projects and neglect of other responsibilities of the Office of Recombinant DNA Activities. Compared to the importance of uniform application of the guidelines, both to protect the public and the environment and to establish common ground rules in a highly competitive research area, neither argument is persuasive.

In answer to a question posed by Senator Kennedy earlier this year, Dr. Fredrickson stated that ORDA review of original memoranda of understanding and agreement and modifications of ongoing research grants "generally is completed in two to five days." Longer delays have been occasioned by transmittal of protocols through the individual Institutes of NIH, a problem that would apparently be corrected by the proposal to relieve the Institutes of responsibility to review compliance with the guidelines. The argument that ORDA should devote more time to interpretation of the guidelines and communication with researchers suggests that there will not be prompt and thorough review of protocols which are required to be submitted after research has commenced.

Inconsistency in institutional interpretations of the guidelines seems inevitable. The director of ORDA recently indicated that as many as 15% of locally approved MUAs have contained substantive errors, including errors of classification. Dr. Fredrickson implies that this is a price that should be paid for institutional responsibility.

I do not suggest that authority to approve even minor changes in experiments should remain at the Federal level. I do recommend, however, that prior NIH approval be required wherever the appropriate containment levels may be subject to different interpretations. If no judgment is required to assign containment levels to particular experiments, institutional approval is appropriate. However, NIH should review such actions promptly and require correction of any errors within a specified period of time. The same procedures should be applied to both NIH-funded and privately-supported research projects subject to the guidelines.

Surprisingly, the Federal Register documents contain no indication that there have been two thoroughly investigated violations of the guidelines. One involved the use of a vector prior to its certification by NIH and continuation of the experiment for some time after discovery of the error. In the other case, research proceeded for several months without an approved MUA. In both instances, the institutional committees as well as individual investigators were at fault. The duties of IBCs in section IV are described in much too general terms. More detailed expectations must be

realistic, however; part-time members of institutional committees are not likely to have sufficient time and motivation to monitor experiments frequently or to investigate violations thoroughly. I recommend that NIH conduct periodic audits of the conduct of institutional biosafety committees and have authority to suspend a committee with a record of bad performance. In such cases, the responsibilities of the committee would revert temporarily to NIH.

Non-trivial violations of the guidelines and accidents should be reported promptly to both the institutional committee and the Office of Recombinant DNA Activities. NIH should not rely solely on the institution to investigate an allegation of a serious violation. The guidelines should make clear that funds will be suspended or terminated if such a violation is found to have occurred. Institutions should be encouraged to develop procedures for disciplining individual offenders.

5) Representation

It is important for the Director of NIH and the heads of institutions to have discretion in appointments to the Recombinant DNA Advisory Committee and the institutional biosafety committees. Nonetheless, I believe that NIH should make a more definite commitment to broader representation on these committees. The Subcommittee's report recommends that the RAC should be expanded to include members with expertise in regulatory procedures,

safety and health regulation, and laboratory work. The number of lay members should be increased in view of the social implications of the research. Institutional committees should include scientists not engaged in recombinant DNA work, representatives of laboratory workers, and public members not affiliated with any institution conducting recombinant DNA research.

6) Training

It is generally agreed that day-to-day compliance with the guidelines depends far more on training in microbiological techniques than, for example, external monitoring. The forthcoming report of the American Society for Microbiology should be extremely useful in developing general standards for training and curricula for Federally-sponsored training programs, which would not be limited to recombinant DNA research. In addition, there must be an assessment of whether investigators and technicians meet those standards. Institutional committees should be required to report to NIH periodically the qualifications of researchers and laboratory personnel. NIH, in cooperation with institutions, should develop procedures to ensure that they receive adequate training.

NATIONAL SCIENCE FOUNDATION
WASHINGTON, D.C. 20550

OFFICE OF THE
ASSISTANT DIRECTOR
FOR ASTRONOMICAL,
ATMOSPHERIC, EARTH,
AND OCEAN SCIENCES

October 16, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

The National Science Foundation (NSF) has reviewed the Environmental Impact Assessment of the Proposed Revised Guidelines for Recombinant DNA Research, as published in the Federal Register on 28 July 1978. The following comments are offered on that section of the proposed guidelines contained on pages 33096 through 33178.

The Environmental Impact Assessment appears to be a thorough and fully documented analysis reflecting that the revisions are designed to insure that recombinant DNA research will be conducted under standards of safety based on the latest scientific knowledge, and in a manner that provides maximum protection for the public and the environment. The document accurately describes the technical aspects of recombinant DNA research, its conjectural risks and benefits. For each section the current guidelines are analyzed and alternative proposals from public commentators are analyzed. The presentation is complete, objective, and thoroughly documented with references and appendices.

The NSF concludes from the analysis that the implementation of the proposed revised guidelines will produce no significant environmental impact.

Sincerely yours,

Daniel Hunt
Deputy Assistant Director

NATIONAL SCIENCE FOUNDATION
WASHINGTON, D C 20550

October 17, 1978

Dr. Donald Fredrickson
Director, National Institutes of Health
Bethesda, MD 20014

Dear Don:

The purpose of this letter is to develop more fully the NSF position on the proposed revised guidelines for recombinant DNA research. Since I did not take advantage of the opportunity to do this at the end of the recent Interagency committee meeting, I fear you may have the impression that I am satisfied with the procedures you described. This would be a false impression.

I did not speak up at the end of the meeting for two reasons. First, I had already spoken longer and more critically than the representatives from the other agencies. Secondly, the final minutes of an Interagency committee meeting was neither the time nor the place to argue that the NSF has a different role and responsibility with respect to recombinant DNA research activity than most, if not all, of the other agencies represented at the meeting. Research and non research oriented agencies have different roles to play and different contributions to make with respect to implementing the guidelines. NSF support of research involving recombinant DNA techniques relative to that of the NIH is not trivial, but significant. Indeed, in this respect we differ from the other research oriented agencies. We have a large constituency to whom we have a responsibility. It is not obvious to me, why you do not recognize our special role and why you do not wish to share with us more meaningfully implementation of the technical aspects of the guidelines.

In your telephone call to me in the morning of the day of the meeting you asked me to listen carefully to the "new" roles and responsibilities of RAC and the IAC before presenting the NSF position. I did listen carefully, but do not think your discussion of new "procedures" was responsive to Dr. Atkinson's letter regarding the

proposed revised guidelines nor did I hear anything meaningfully new. You emphasized that you were transferring to RAC much of the responsibility the PRG designate to the Director of NIH, but in essence you did not indicate an intention to delegate any authority to RAC. As I heard it, you merely indicated RAC has a wide range of areas within which it can make recommendations for consideration by the director of NIH. Similarly, I was not impressed with the enhanced roles and responsibilities implied in the suggestion that the approximately twenty agencies represented on the IAC designate liaison members to RAC. RAC meetings have been primarily technical in nature and will be even more so henceforth. It is a nice gesture to encourage all these agencies to join the research agencies that already have liaison members to participate in RAC meetings, but the suggestion must be recognized as only a gesture.

The recent interagency meeting was a good vehicle to permit you to state publicly that there is general agreement among the agencies with your reaction to agency comments to the PRG, but it was not a good vehicle to discuss the PRG meaningfully. I suppose the purpose of the meeting was the former and not the latter. Nevertheless, it must be observed that experience of the last 2-1/2 years has taught us that procedural aspects or implementation of the guidelines are intrinsically linked to technical aspects of the guidelines and it is stacking the deck to use the IAC consisting mostly of nonresearch agencies to seek general agreement with the roles and responsibilities prescribed in the revised guidelines. To consider the NSF in the same light as Labor, Justice, Transportation, and other non-science agencies reflects an insensitivity that must not go unheeded. As NSF's senior scientist for recombinant DNA activities I had been a voting member of RAC during most of the period in which the current guidelines were developed and was moved to a liaison role to make a slot available for a nonscientific member. With this history, it is very unflattering to know you believe you are extending the role and responsibility of the NSF by permitting us to have a liaison member in RAC together with representatives from nonscientific agencies such as the naive person who asked for clarification about the difference between "recombinant DNA" and "recombinant DNA molecule" as referred to in different places in the PRG. It should not be necessary to explain to you the differences in roles and responsibilities between the NSF and DOT in our respective roles past, present, and future. Similar differences exist between NSF on the one hand and each of the other liaison agencies.

In your telephone call to me on the morning of October 12, you stated that Dr. Atkinson's recommendation of an "interagency subcommittee" considering RAC recommendations would not work. Your concern was that EPA and OSHA would insist on being members of the subcommittee and this would complicate the process. But an IAC subcommittee is not a proper interpretation of the NSF recommendation. Representation of two or possibly three of the other research supporting agencies on your "kitchen cabinet" would be a more accurate interpretation of Dr. Atkinson's recommendation. It is important that you be exposed to points of view of agencies other than NIH when evaluating RAC recommendations. Further, an important part of Dr. Atkinson's recommendation that I emphasized at the meeting is the need to reduce the time lag between RAC recommendations and their implementation. If the NSF had representation when RAC recommendations were evaluated, and we understood the basis of postponement of decisions, we undoubtedly would be more patient with the delays involving NSF supported research.

I will close by stating that if the NIH accepted the NSF in a closer partnership role with respect to implementing RAC recommendations, I feel confident that role would be supportive of NIH leadership. I look forward to discussing more fully with you the NSF position on the proposed revised guidelines before the final revisions are determined. With best personal wishes.

Sincerely yours,

Herman W. Lewis
Senior Scientist for
Recombinant DNA

FRIENDS OF THE EARTH

620 C STREET, S.E., WASHINGTON, D. C. 20003

(202) 543-4313

DAVID BROWER, *President*

October 23, 1978

Mr. F. Peter Libassi,
General Counsel
Department of Health, Education, and Welfare
200 Independence Ave. SW Rm. 722 A
Washington, D.C. 20201

Dear Peter,

To begin, I would like to thank you again for the opportunity to present our views on the procedural aspects of the proposed revised guidelines for recombinant DNA research. The overwhelming opinion of all those who have been involved since the public hearing on September 15th, is that our concerns are finally being "heard." Some of us are even optimistic enough to believe that our suggestions may even be implemented. This is a very different climate than that to which we have become accustomed, and I wish to thank you and Secretary Califano for your concern and commendable involvement. We sincerely hope that HEW's oversight will not end with these deliberations; we have found it a considerable improvement over the NIH.

I would like to briefly outline our position on the institutional biosafety committees as it was discussed in our meeting on October 18th, taking into account your comments.

We are also painfully aware of the unsatisfactory nature of present federal regulatory mechanisms, and do view the IBC as a worthwhile experiment to be supported. On the other hand, it will never work unless the membership is carefully balanced to avoid the "fox guarding the chicken coop" problem. I think you understand our concerns, and I will not further elaborate other than to refer you to my testimony for one possible model, and to reiterate that no matter what the specified make-up, if the institution chooses all the members, the best laid plans can and will be circumvented.

Assuming the make-up of the biosafety committees is more to our liking, we still have problems with the <u>particular</u> authority that has been delegated to the IBC's. We could support increased inspection authority at the local level as a much more effective alternative to a federal inspection team. Members of the IBCs or its agent, the biological safety officer (BSO) should be required to inspect the labs on a regular basis.

While that particular job is not given to them in the guidelines, the type of authority (assessment of risk) that is being delegated is inappropriate at the local level for the following reasons:

Committed to the preservation, restoration, and rational use of the ecosphere

1. IBCs do not necessarily have access to the expertise required to make the determinations of potential risk.

2. IBCs are even closer than the NIH to those who are in the biggest hurry to proceed. The pressure that will be placed on a "recalcitrant" member should not be underestimated.

We have no problem with IBC approval of changes which clearly could present "no significant risk", but feel strongly that changes in location, principal investigator, and particularly changes in biological materials (host-vector systems or source of DNA) are important enough to warrant prior ORDA approval. Furthermore, no researcher should be allowed to switch to the recombinant DNA technique without prior NIH review.

There is simply no compelling rationale for these changes that a special "expedited ORDA procedure" could not address as easily and with much more safety.

An expedited ORDA procedure could also be developed to approve single step reductions in containment levels which meet the "no significant risk" criteria. "Free of harmful genes," we hope you will agree, is a terrible standard, particularly for interpretation by several hundred local committees.

To reiterate:

1. Allow the IBCs to do what they are best suited for, local oversight and inspection.

2. Develop a "priority procedure" for significant changes in ongoing projects and for approval of lowered containment levels.

3. Allow IBCs to approve "non-significant" changes in protocols.

4. Give IBCs the authority to raise containment for safety reasons related to local conditions.

One other point I feel worth repeating relates to training which is probably the single most important aspect to insure the safety of this research. Biological safety officers should be required to attend a NIH training seminar which should teach them:

1. How to train others in standard microbiological technique.

2. Emergency procedures.

3. Health monitoring and uniform record-keeping

The guidelines should then clearly delegate these responsibil-

ities to the BSO. The more clearly this authority is delineated, the more confidence we will have in its eventual implementation. BSOs should be required at all institutions doing recombinant DNA research.

In closing, I would like to thank you again for your even-handed manner and willingness to listen to our concerns. We eagerly await the final promulgation of the guidelines fully expecting to see your imprint on them.

Your staff tells me you've been working too hard, which is not hard to believe even if you were only working on DNA and low level radiation. Take a long vacation. You deserve it.

Best regards,

Pam

Pamela Lippe
Assistant Legislative
Director

cc Jim Hynchman
Joe Perpitch

NATIONAL DIABETES ADVISORY BOARD
BETHESDA, MARYLAND 20014

Mailing Address: P.O. Box 30174
Office: 7550 Wisconsin Avenue, Room616
Telephone: (301) 496-6045

October 23, 1978

Dr. Donald S. Fredrickson
Director, National Institutes of Health
Building #1, Room 124
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

The Insulin Study Committee of the National Diabetes Advisory Board submitted its Report to Congress in June of 1978. Needless to say, we are grateful for your participation in the analysis of the problem and your part in the development of the Report. The Recommendations within the Report to the various government agencies were formulated after a detailed survey of the available data, testimony taken from expert witnesses, and much discussion and analyzing of the accumulated information by committee members, staff, consultants and members of the National Diabetes Advisory Board.

The Recommendations to the National Institutes of Health contained within the Report on pages three and four is as follows:

> To obtain the information needed for its report, the National Diabetes Data Group should be responsible for assembling the data in collaboration with the Food and Drug Administration, the Federal Preparedness Agency, the Department of Agriculture, the National Center for Health Statistics, the Department of Commerce, the National Institutes of Health, the Center for Disease Control, and the private sector.
>
> Recombinant DNA Technology
>
> The Insulin Study Committee has determined that the successful application of recombinant DNA technology could result in a virtually limitless supply of insulin. Therefore, the Committee recommends that research on the development of synthetic insulin production by means of this technology should continue and should be encouraged by the Federal and private biomedical research community.

> The Committee urges that Congress, as it considers legislation to provide for DNA safety regulation, and the National Institutes of Health, as it considers the modification of existing guidelines, recognize that unnecessarily restrictive requirements could impede the progress of this essential research on synthetic insulin.

For inclusion in the 1978-79 National Diabetes Advisory Board Report to Congress, could you prepare for us a paper outlining what steps will be taken by your institute to follow-up on the Recommendations made by the Insulin Study Committee. We would appreciate an update on what you have already accomplished based on the committee's recommendations. In addition, please feel free to add any comments or conclusions or further recommendations, which you have found to be pertinent to the subject of the study of insulin supply and demand in the United States from 1978 - 2000.

Please forward by November 5 the information on the status of the Recommendations in your institute so that we may include the data in our Insulin Study Committee update within the National Diabetes Advisory Board 1978-79 Report to Congress.

Sincerely,

Lee Ducat

Lee Ducat, Chairman
Insulin Study Committee
National Diabetes Advisory Board

LD/sb
Enclosures: A Study of Insulin Supply and Demand and Appendix.
Recommendations - Supply and Demand of Insulin in the United States.
Human Insulin Article.

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October 25, 1978

Dr. Donald S. Fredrickson
Director
National Institute of Health
Bethesda, MD 20014

Dear Dr. Fredrickson:

We are writing to expand upon our earlier comments regarding enforcement of recombinant DNA research guidelines. In our last letter, we suggested a number of alternatives to the necessary but inflexible sanction of fund termination. In addition to those alternatives, the Guidelines should provide for local sanctions to be imposed by the institution against the principal investigator or other researchers.

It is also imperative that the Guidelines: 1) explain what steps must be taken to notify NIH of violations; 2) explain the impact of violations upon ongoing research; 3) establish procedures and time limits for resolution of complaints; and 4) provide for enforcement by private parties.

Violations of the guidelines will be discovered either by the researchers themselves, by the institution at which the research is being conducted, by NIH review of IBC decisions or by NIH investigation of complaints from other sources. The Guidelines should require the principal investigator and other researchers immediately to notify the IBC of any violations and stop operations until the violation is corrected. Similarly, when violations, are discovered either by the institution or by NIH, immediate cessation of operations should be required. It would be foolhardy to allow operations to continue pending completion of administrative procedures. While it may be possible for NIH to identify some specific minor technical violations which would not warrant cessation of operations in cases where such a cessation would jeopardize major research investments, such exceptions should be established only after additional notice and comment, and should be clearly described in the regulations. Indeed, even if it is decided that additional flexibility is needed to permit continuation of some experiements in the face of violations which do not fall within such express exceptions, the Guidelines should at a bare minimum provide that such continuation may be permitted only if the Director of NIH certifies that continuation poses no danger under the circumstances.

The Guidelines should also contain clear procedures for filing and processing of complaints, including rigorous time limits for investigation, issuance of notice of findings, conduct of administrative hearings where appropriate, and initiation of enforcement action. Provisions should be made for expedited review and enforcement in any case where research is permitted to continue pending correction of violations or satisfactory resolution of disputed complaints.

We fully understand the concern that a complaint procedure may sometimes prevent decision makers from allocating resources effectively, and we agree that a great deal of thought needs to be given to devising other enforcement mechanisms. Nevertheless, the shortcomings which often accrue to complaint mechanisms are peculiarly absent when such a procedure is applied to the rather unique problems of recombinant DNA research. In this particular field, even given the exigencies of tight budgets and scarce resources, we doubt the Department would ever need to choose between conducting general compliance reviews and processing individual complaints, or between investigating widespread instances of systemic violations and resolving allegations affecting only a few people. Because the potential dangers the Guidelines are intended to prevent are so vast and irreversible and because each violation will by its very nature threaten large numbers of people, we expect the number of violations to be relatively small and the importance of investigating each complaint to be great.

The Guidelines and the MUA should also specify that any person who may be adversely affected by research violations will be considered a person aggrieved, with the right to pursue administrative remedies through a complaint and hearing procedure. Moreover, the MUA should specify that it is a contract intended to benefit all third parties who may be affected by violations. This will permit private parties to initiate legal action to enforce the provisions of the MUA. Without such a provision, there will be no safety valve to prevent future administrators from disregarding the Guidelines or to stop experiments which are being conducted irresponsibly. Such a safety valve is especially essential where, as here, a short period of neglect could result in an incomparable disaster.

With thanks for the consideration you and the other members of the Review Committee have given our previous comments,

Sincerely yours,

Sanford A. Newman
Herbert Semmel

SAN:vl
cc: F. Peter Libassi
Jim Hinchman

COPY

NATIONAL SCIENCE FOUNDATION
WASHINGTON, D.C. 20550

October 25, 1978

Dr. Joseph G. Perpich
Office of the Director
National Institutes of Health
Bethesda, MD 20014

Dear Joe:

During our telephone conversation earlier this week I made the point that the proposed revised guidelines were written primarily with NIH supported research in mind which prompted you to ask what specific statements the NSF had problems with.

I realize that extensive rewriting at this time is not desirable, so I have annotated the enclosed eight pages of the proposed revision in a manner that will require a minimum of rewriting. In fact, except for the short substitution statement (P. 33086: IV-B-1-a), the suggestions can be incorporated into the revised guidelines with a footnote or two. If the guidelines are silent on the phrases struck out in blue ink on P. 33086, no principles are violated but desired flexibility is added.

If these suggestions are accepted it will make NSF implementation of the revised guidelines simpler to announce and do much to reduce potential confusion in the scientific community. I cannot emphasize too strongly how seriously the NSF feels its responsibility to the research it supports, including resistance to even the appearance of regulation by another agency in the guise of guidelines.

Sincerely yours,

Herman

Herman W. Lewis
Senior Scientist for
Recombinant DNA

Enclosure

cc: Dr. Fredrickson
Dr. Omen

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October 25, 1978

Donald Fredrickson, M.D.
Director
National Institutes of Health
Bethseda, Maryland 20014

Dear Dr. Fredrickson:

I want to pass on to you a statement prepared by my staff about the proposed revised guidelines on recombinant DNA research published in the Federal Register, July 28, 1978. I fully endorse its conclusions concerning proposed changes, and I agree that principal responsibility for ensuring compliance should be borne by the institutions where the research is being done.

Please be assured that the University, through its investigators, its institutional Biosafety Committees, and the Administration is prepared to carry out the expanded institutional responsibilities required by the proposed guidelines.

Sincerely,

David S. Saxon
President

Attachment

cc: Chancellors
Executive Assistant David A. Wilson

10-25-78

TO: PRESIDENT SAXON

FROM: Executive Assistant Wilson

RE: Proposed Revised Guidelines, Recombinant DNA Research, Federal Register, July 28, 1978

I developed this statement, based on staff analysis and consultation with the Chancellors, to let you know the reasons for my positive reaction to the proposed changes in direction contained in the revised guidelines. I believe it will be of interest to Director Frederickson of NIH.

The proposed revised guidelines represent a substantial improvement over the original guidelines in that they are responsive both to the continuing need for appropriate safeguards and to the considerable experience of scientists since the earlier guidelines were issued. This experience suggests that the fears of potential risks from recombinant DNA research were exaggerated, and that the practical benefits from such research through improved understanding of biological processes and varied applications in such fields as medicine, industry and agriculture are potentially very promising.

Implementing the guidelines has proven to be a complex, expensive, and time-consuming process which the proposed revised guidelines try to simplify and make flexible. The changes should be advantageous for scientific research. Specifically I refer to the reduction in levels of containment for certain experiments; delegation of primary responsibility for compliance to the institution where the research takes place; exempting from the guidelines experiments which pose no threat to safety; providing for deregulation of other experiments when indicated; permitting certain risk-assessment studies which will enhance knowledge of potential hazards; clarifying the streamlining procedures for permissible experiments.

As a result of these changes the institutions through Institutional Biosafety Committees (IBCs) will have principal responsibility and authority for determining and monitoring compliance. This means the University and NIH must be clear about their separate and joint responsibilities and must respond expeditiously to the standards that have been established. On this latter point I want to suggest a change in the proposed revised guidelines brought to my attention by an IBC member. Section V B of Appendix C (p. 33094) should include guidance to an IBC through inclusion of some examples of criteria that have been used in the past in granting single step reductions in physical or biological containment levels. This will assist IBCs to achieve consistency in their interpretation and approval practices.

The proposed revised guidelines at the same time seem better able to protect health and safety and the environment. Their applicability has been expanded to include all recombinant DNA research at an institution receiving NIH funding irrespective of the source of funding for the research, and they now provide for private industry participation on a voluntary basis. Membership on an IBC now must include at least one public member and for institutions with investigators engaged in relatively high risk experiments, a biological safety officer. In addition, sanctions are now available to NIH to suspend, limit or terminate grants in response to non-compliance which may be useful.

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October 26, 1978

Donald S. Fredrickson, M.D.
Director
National Institutes of Health
Building 1, Room 124
9000 Rockville Pike
Bethesda, Maryland 20014

Dear Don:

On two earlier occasions I have reviewed proposed guidelines for recombinant DNA research and have provided my comments on them. Further revisions were proposed in the existing guidelines in the Federal Register on July 28, 1978 (43 F.R. 33042). Regrettably, I left for vacation just as they were released and have not had an opportunity to study them since my return until this past weekend. Although I am aware that the time for public comment has expired, I am nonetheless submitting these brief comments in the hope that they may be useful to you. If their lateness precludes your consideration of them I will understand completely.

My two earlier letters considered the legal and conceptual bases for the regulation of recombinant DNA research. There is no need for me to reiterate those comments except again to emphasize that any regulation of research should remain flexible and never become static. As more information demonstrating the safety of this research becomes available, the guidelines should be revised accordingly until, hopefully, some day the need for regulation may disappear completely.

In general, I believe the latest proposal is a faithful reflection of the consensus of views stated at the last

public hearing, conducted on December 15-16, 1977. In many respects, this proposal is a distinct improvement both over the last proposal and over the current guidelines.

One particular problem, however, continues to exist. The administrative procedures incorporated in the guideline still contain significant deficiencies. It is this aspect of the latest proposal on which I again wish to offer comment.

First, nothing in the guidelines (as contrasted with the preamble to the guidelines) relates to the composition or selection of the Recombinant Advisory Committee (RAC). Nor does any provision in the guidelines inform the public how future changes in the guidelines can be proposed and considered. I continue to believe that very simple provisions which explicitly state that NIH will solicit nominations for the RAC from all interested persons, that there will be "public" members of the RAC as well as expert scientists, and that changes in the guidelines can be suggested by petitions from interested lay persons or scientists, would be very helpful additions.

Second, I continue to find the administrative procedures unclear and confusing. The language appears to be different for each procedure, thus raising uncertainty whether all of the procedures are indeed intended to be different or are in fact similar or identical to each other. Standardized language should be adopted for standardized procedures. In addition, some of the proposed procedures appear to be needlessly stringent and to preclude legitimate flexibility. Finally, the rationale for the different procedures adopted for the various different administrative actions is nowhere stated, which may account for what appears to me to be a lack of consistency among these procedures.

Approaching the matter conceptually, there appear to be two possible sources of action under the guidelines: the Director or the RAC. (Section II(D)(ii)(a) states that certification of a host-vector system is actually done by "NIH" but I assume that this will be changed. NIH must act either through the Director or the RAC.) Action taken by the Director can, in turn, be taken in four ways: after notice and comment, after notice but before the comment is received and analyzed, without any notice or comment but upon the advice of the RAC, and without any notice or comment or advice by the RAC.

For exemptions and large scale experiments, Sections I(E)(5) and I(D)(6) seem to permit action by the Director only after notice and comment, thus precluding immediate action. In my judgment that is far too inflexible. Even the Administrative Procedure Act recognizes valid exceptions, which permit action to be taken after notice but before the comment is received, in the public interest. Thus, at the very minimum I believe that any notice-and-comment procedure should always provide for exceptions to permit expedited action in the public interest. (You should also spell out what kind of "notice" is intended. Unless you specify otherwise, it will be interpreted, as I interpret it, to require Federal Register publication.)

Section III states, in the second paragraph, that biological and physical containment provisions can be changed by the Director. There is no requirement of notice and comment or of consultation with the RAC. I can see no rationale for changing these provisions in an entirely flexible and free way, while permitting exemptions and large scale experiments only after the most stringent procedures. If there is a rationale for these differences, it should be stated. I favor, of course, far greater flexibility in all of the procedures.

These are only examples of the problems that I continue to find in the administrative procedures proposed revision of the guidelines. I would strongly urge that all of the procedural provisions be reviewed very carefully for flexibility and consistency. I would again urge that provision be made for variances for individual experimentation immediately upon public notice whenever the Director concludes that this would advance the interests of science and the public without any significant health hazard. This would prevent any criticism that the guidelines were unnecessarily hindering scientific creativity.

Finally, I wish to express my continuing support for the superb work that NIH has been doing on these guidelines. While I have had some questions about their content, I have never had the slightest doubt about the need for the guidelines and the high quality and integrity of those who have been working so hard on them.

Sincerely yours,

Peter

Peter Barton Hutt

PBH/mh

the University of Alabama in Birmingham / UNIVERSITY STATION / BIRMINGHAM, ALABAMA 35294

the Medical Center / DEPARTMENT OF MICROBIOLOGY / October 27, 1978

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Don:

I just returned from attending the sixth course on Biohazard Containment and Control for Recombinant DNA Molecules which was held at the Frederick Cancer Research Center and where I participated as one of the course lecturers. At this meeting, I learned that you received numerous comments concerning the containment requirements for cloning primate, mammalian and avian DNAs in E. coli K-12 host-vector systems; more specifically, that P3 + EK1 be allowed as an alternative to P2 + EK2. I was also informed that this question has been referred to the Recombinant DNA Advisory Committee, which is meeting in Frederick next week. In my letter to you of September 23, 1978, I specifically made no comments about the required levels of containment for the above-mentioned types of experiments, since I wholeheartedly concurred with the reasons for not allowing the option of P3 + EK1 in lieu of P2 + EK2. Therefore, the purpose of this letter is to indicate the reasons for my support for maintaining the P2 + EK2 containment levels as now stipulated in the proposed revised Guidelines.

Two objections have been made to the use of EK2 host-vector systems. One of these concerns the limited number of EK2 systems available and the other concerns the ease with which these systems can be used. The first objection is very real and my laboratory group is endeavoring to remedy this situation. Nevertheless, a diversity of EK2 systems with different mutational defects in host strains is much more necessary when cloning DNA from prokaryotic and lower eukaryotic organisms, where it is possible to select for expression of donor DNA sequences that specify a product to complement a genetic defect in the host strain than when cloning DNA from mammalian and avian sources since it is quite dubious that any gene function from higher organisms will be functionally expressed to complement a genetic defect of a prokaryotic host. On the other hand, there is a need for a greater diversity of cloning vectors to facilitate selection for functional expression of higher eukaryotic DNA sequences. These cloning vectors are being constructed in a number of laboratories and obtaining approval for their use with existing E. coli K-12 host strains is a much simpler task than constructing and obtaining approval of an entire host-vector system. This is particularly true when the vector is a modification of an already approved vector such as pBR322. It is thus my opinion that this first objection to the lack of diversity of EK2 host-vector systems is not an important argument to support the option of P3 + EK1 in lieu of P2 + EK2

AN AFFIRMATIVE ACTION / EQUAL OPPORTUNITY EMPLOYER

for cloning of primate, mammalian and avian DNA in E. coli K-12 host-vector systems. The second argument, concerned with the ease with which the EK2 system can be used, is more valid and I think pertains mostly to the use of χ1776, which is a rather fastidious microorganism. Certainly, approved EK2 lambda vector-host systems are no more difficult to use than, and even have some advantages over, currently utilized EK1 lambda-host systems. In terms of the problems that some investigators have had in working with χ1776, persons in our own laboratory, even those who were not involved with the construction of χ1776, have had no difficulty and we have continually developed procedures for improving the ease with which this strain can be used. For example, we have developed a new transformation method which yields 10^7 transformants per microgram of plasmid DNA and have developed methods for amplification of ColE1-derived vectors in χ1776 with yields nearly equal to those obtained with various EK1 hosts. These new methods have been published or in the case of the χ1776 transformation method have been disseminated to those attending the biohazard courses held in September and October as well as to individuals requesting χ1776. I personally believe that some of the difficulty that some investigators have had has been due to failure to read the material sent to them with χ1776 and/or to scientific ineptitude. I should indicate that failure to follow carefully the directions we have distributed with χ1776 or to pay close attention to the properties of the host-vector system leads to difficulty in using the χ1776 plasmid systems for recombinant DNA research and thus has led to complaints on the part of recombinant DNA researchers. On the other hand, a substitution of P3 containment so that one can use EK1 systems is not accompanied by any penalty for scientific ineptitude if the P3 containment facilities and procedures are not functioning and/or are not adhered to since the experiments will still work even if the containment is inoperative at the P3 level. As you are well aware, the people now engaged in recombinant DNA research come from a diversity of backgrounds and the same people who have difficulty in using the χ1776 plasmid vector systems are also the same individuals who have never been adequately trained in medical microbiological techniques and are most likely to not use P3 containment facilities and procedures in the manner prescribed in the Guidelines. I thus respectfully request that you give careful consideration to these points and hope that you finally decide to leave the requirement of P2 + EK2 containment for the cloning of primate, mammalian and avian DNA in E. coli K-12 host-vectors.

Sincerely yours,

Roy Curtiss III

RCIII/pp

THE ROCKEFELLER UNIVERSITY
1230 YORK AVENUE · NEW YORK, NEW YORK 10021

October 30, 1978

Donald S. Fredrickson

Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

One of my colleagues at Rockefeller University showed me yesterday his copy of "Comments of the Natural Resources Defense Council, Inc. on the Proposed Revision of The National Institues of Health's Guidelines on Recombinant DNA Research," which was mailed to you on September 19, 1978. As I am a member of the Board of Trustees of NRDC, you may have assumed that I had been consulted about the preparation of this document and that I am in favor of its recommendations. But this is not the case. I had no idea that NRDC was involved in the Recombinant DNA problem, for which it has no competence. I find the text of the "Comments..." misleading because it is grossly unbalanced, and displays a complete lack of understanding of laboratory practices. The recommendations would make more sense if they recommended a complete interruption of DNA Recombinant Research.

On several occasions during the past two years, I have publicly stated that

a) the dangers of DNA recombinant research have been greatly exaggerated and can be avoided by commonsense laboratory techniques, and

b) this kind of research is so promising of important theoretical and practical results that it would be an anti-social act to paralyze it by useless regulations. My views on these matters have been presented in widely-read publications such as

--the Op-Ed page of the New York Times, a piece entitled "Genetic Engineering" in April, 1977.

--my book The Professor, The Institute and DNA (Rockefeller University Press, 1976), p. 228.

Failure on the part of NRDC to communicate with me--a member of its Board of Trustees familiar with the technical aspects of recombinant DNA research--reveals either an irresponsible lack of familiarity with the literature in this field, or for intellectual dishonesty in using my name for a cause that I regard as ridiculous.

For these reasons, I am resigning today my membership in the Board of Trustees of NRDC.

Sincerely,

René Dubos

René Dubos

November 17, 1978

Dr. Rene Dubos
Professor Emeritus of
Environmental Medicine
The Rockefeller University
1230 York Avenue
New York, New York 10021

Dear Dr. Dubos:

Thank you for your letter of October 30. From our brief conversation when you were at NIH for the Nutrition Conference, and also from reading both your Op. Ed. piece and most enjoyable book on Avery and DNA, I knew that you did not endorse the comments of the Natural Resources Defense Council on the recombinant DNA guidelines.

Believing myself devoted to the original aims of the environmental movement, I, too, am appalled at its recent descent into sterile proceduralism. Yet, your resignation from the Board of Trustees of NRDC is at once gratifying and disturbing to me. Without the continued influence and participation of such persons as yourself, who is to save the salvationists?

With my great respect and kindest regards,

Sincerely,

/s/ Donald S. Fredrickson, M.D.
Donald S. Fredrickson, M.D.
Director

THE ROCKEFELLER UNIVERSITY
1230 YORK AVENUE NEW YORK, NY 10021

November 1, 1978

JOSHUA LEDERBERG
PRESIDENT

Mr. Peter Libassi
Department of Health, Education
and Welfare
200 Independence Avenue, S.W.
Washington, D. C. 20203

Dear Mr. Libassi:

I understand that Marcia Cleveland and Louis Slesin of the Natural Resources Defense Council made certain comments, undercover of a letterhead dated September 19th, critical of the proposed mitigation of the NIH Guidelines for Recombinant DNA Research (43 FR 33042, July 28, 1978).

These comments were submitted on the stationery of the Natural Resources Defense Council where my name also appears as a member of the Board of Trustees.

A number of my colleagues have expressed surprise - and quite correctly and understandably so -- at my apparent association with these criticisms. My own position opposing unduly stringent regulation in this area was expressed quite clearly several years ago, and I have had no reason whatever to alter my earlier opinions on the matter. The fact is that as a member of the Board, I strongly applaud the general purposes of the NRDC but I have not approved nor taken any part in this staff paper: a relationship which is by no means unusual although often misunderstood.

To avoid any possible misunderstanding I believe it important that I put on the record my personal disavowal to this particular comment.

Yours sincerely,

Joshua Lederberg

Joshua Lederberg

cc: Mr. John Adams
Miss Marcia Cleveland

bcc: Dr. Donald Fredrickson ✓
Dr. Allan Campbell
Dr. Norton ZInder

NEW YORK UNIVERSITY MEDICAL CENTER
School of Medicine
550 FIRST AVENUE, NEW YORK, N.Y. 10016
AREA 212 679-3200
CABLE ADDRESS NYUMEDIC

Department of Pediatrics

December 8,1978

William J. Gartland, Jr., Ph.D.
Director
Office of Recombinant DNA Activities
National Institute of General Medical Sciences
Department of Health, Education & Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Garland,

I am writing to you on behalf of the Society for Pediatric Research (SPR) concerning the Proposed Revised NIH Guidelines for Recombinant DNA research. Unfortunately, the document reached us too late for comments. However we would like to register an offical opinion. After careful reading of the regulations the SPR feels that these guidelines are lucid, concise, and excellently formed. We heartily endorse them.

Would you kindly send me a copy of the final guidelines and let me know when they will (or did) appear in the Federal Register.

Thank you.

Sincerely yours,

Anne Gershon

Anne A. Gershon, M.D.
Associate Professor
of Pediatrics

AAG:MGC
CC: Dr. JoAnne Brasel, President, SPR
Dr. John Johnson, Secretary Treasure, SPR

APPENDIX B

(Re: Civil Action No. 77-2225; Friends of Earth, Inc., v. Califano et al.)

	Page
U.S. District Court for the Southern District of New York	
Summons.	B-2
Answer	B-45

[This appendix contains the summons and answer of the still-pending case of Friends of the Earth v. Califano et al., alleging the failure of the defendants to comply with the National Environmental Policy Act in issuing the NIH Guidelines in June 1976.]

SUMMONS IN A CIVIL ACTION

CIV. 18 (2-64)
(Formerly B.C. Form No. 60a Rev. (6-49))

United States District Court

FOR THE

SOUTHERN DISTRICT OF NEW YORK

CIVIL ACTION FILE NO. _____

FRIENDS OF THE EARTH, INC.,

Plaintiff,

- against -

JOSEPH A. CALIFANO, JR., individually and as SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, JAMES F. DICKSON III, M.D., individually and as ASSISTANT SECRETARY FOR HEALTH OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, DR. DONALD S. FREDRICKSON, individually and as DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH, and THE NATIONAL INSTITUTES OF HEALTH,

Defendant S.

SUMMONS

To the above named Defendants :

You are hereby summoned and required to serve upon Richard M. Hartzman

plaintiff's attorney , whose address is; Friends of the Earth, Inc.
72 Jane Street
New York, New York 10014,

an answer to the complaint which is herewith served upon you, within 60 days after service of this summons upon you, exclusive of the day of service. If you fail to do so, judgment by default will be taken against you for the relief demanded in the complaint.

_____
Clerk of Court.

_____
Deputy Clerk.

Date: MAY 9 1977

[Seal of Court]

NOTE:—This summons is issued pursuant to Rule 4 of the Federal Rules of Civil Procedure.

JUDGE BRODERICK

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

----------x

FRIENDS OF THE EARTH, INC.,

Plaintiff,

- against -

JOSEPH A. CALIFANO, JR., individually and as SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, JAMES F. DICKSON III, M.D., individually and as ASSISTANT SECRETARY FOR HEALTH OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, DR. DONALD S. FREDRICKSON, individually and as DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH, and THE NATIONAL INSTITUTES OF HEALTH,

Defendants.

----------x

Civil Action No.

77 Civ. 2225

VERIFIED COMPLAINT FOR DECLARATORY JUDGMENT AND INJUNCTION

Plaintiffs, as and for their complaint, by their attorney named below, allege as follows:

1. This action is brought against the above-named defendants for their failure to comply with the requirements of the National Environmental Policy Act of 1969 (NEPA), P.L. 91-190, 83 Stat. 852, 42 U.S.C. §4321 et seq., as amended by P.L. 94-83, 89 Stat. 424; the requirements of the Administrative Procedure Act (APA), 5 U.S.C. §551 et seq. (original version at P.L. 79-404, 60 Stat. 237); and numerous other laws and regulations (a) with respect to the funding of recombinant DNA research and its profound environmental impacts and consequences, (b) with respect to the Recombinant DNA Research Guidelines promulgated by the defendants to regulate the recombinant DNA research program, and (c) with respect to the proposals for legislation regulating recombinant DNA activities.

Plaintiff seeks, inter alia, a declaration from the Court:

A. That the actions of the defendants in connection with the recombinant DNA research program, including the actions and determinations

(1) to conduct recombinant DNA research;

(2) to make grants to individuals and institutions for the purpose of conducting recombinant DNA research;

(3) to let contracts for the construction and renovation of facilities for the conduct of recombinant DNA research;

(4) to promulgate Guidelines for the regulation of the recombinant DNA research program;

(5) to propose legislation regulating recombinant DNA activities;

have been and are contrary to the requirements of law:

B. That the defendants are required by §102(2)(C) of NEPA to prepare and circulate for comment a detailed final environmental impact statement with respect to and prior to the taking of each of the actions and determinations stated above, and that the defendants have failed to prepare and circulate for comment a final environmental impact statement on all of the actions and determinations stated above in contravention of the law:

C. That the defendants are required by §553 of the APA to give notice of a public rulemaking proceeding, provide an opportunity for public comment, and hold public hearings with respect to the promulgation of guidelines for the regulation of recombinant DNA research, and that the procedure followed by the defendants in promulgating the Recombinant DNA Research Guidelines are contrary to these requirements and defective and insufficient as a matter of law:

D. That the defendants are required by §5 of the Federal Advisory Committee Act (FACA), P.L. 92-463, 86 Stat. 770, 5 U.S.C. App. I, October 6, 1972, to have balanced and independent advisory committees, and that the Recombinant DNA Molecule Program Advisory Committee established by the defendants is not balanced and independent, and its membership is contrary to these requirements and defective as a matter of law.

I. JURISDICTION

2. A. This action arises under:

(1) 28 U.S.C. §§1331(Federal question); 1332 (Diversity of Citizenship); 1343(Civil Rights); 1361(Mandamus); 2201 and 2202 (Declaratory Judgments);

(2) 42 U.S.C. §§4331-4347 (NEPA);

(3) 5 U.S.C. §§551-553 and 701-706 (APA);

(4) 5 U.S.C. App. I §5 (FACA);

(5) 42 U.S.C. §§216, 217a, 218, 241, 2421, and 242m (Public Health Service Act);

(6) Executive Order 11514, 35 Fed. Reg. 4247 (March 5, 1970);

(7) 38 Fed. Reg. 10859 (Guidelines for Preparation of Environmental Impact Statements, Council on Environmental Quality, May, 1973);

(8) Part 30, General Administration Manual, Department of Health, Education, and Welfare, November 17, 1973 (Environmental Affairs);

(9) 42 C.F.R. Parts 50 and 52, Regulations of the Public Health Service, Department of Health, Education, and Welfare (Grants);

(10) 45 C.F.R. Part 74, Regulations of the Department of Health, Education, and Welfare (Grants).

B. The amount in controversy herein exceeds $10,000, exclusive of interest and costs.

C. Venue is in the United States District Court for the Southern District of New York pursuant to 28 U.S.C. §1391(e).

II. PARTIES

3. Plaintiff, Friends of the Earth, Inc., is a not-for-profit membership corporation organized and operated under the laws of the State of New York. Its objects and purposes include the preservation, restoration and rational use of the ecosphere and human environment. Friends of the Earth, with worldwide affiliates, has more than 23,000 members nationally, including many members residing close to facilities where recombinant DNA research is being performed under grants from the National Institues of Health (NIH). In addition Friends of the Earth has almost 1500 members residing in the Boroughs of Manhattan and the Bronx of the City of New York, where recombinant DNA research

funded by NIH is being performed at Columbia University, New York University, Yeshiva University and Rockefeller University. The members of Friends of the Earth who reside in New York City and elsewhere are and will be adversely affected and aggrieved by the dangers to their health and the potential disruption of their use and enjoyment of natural resources, which could result from organisms produced in recombinant DNA research.

4. Defendant Joseph A. Califano, Jr., is Secretary of the Department of Health, Education, and Welfare of the United States. Defendant James F. Dickson III, M.D. is Assistant Secretary for Health of the Department of Health, Education, and Welfare of the United States. Defendant Dr. Donald S. Fredrickson is Director of the National Institutes of Health of the Department of Health, Education, and Welfare of the United States. The National Institutes of Health (NIH) is the federal agency authorized to fund and regulate biomedical research under the Public Health Service Act.

III. AS AND FOR PLAINTIFF'S FIRST CLAIM

A. RECOMBINANT DNA RESEARCH.

5. By or about 1973 a scientific technique was developed which enables scientists to propagate novel living organisms by combining the hereditary substance, DNA, from unrelated organisms. This technique has been variously termed recombinant DNA research, gene splicing, gene stitching, molecular cloning, and genetic manipulation, among others.

6. DNA, or deoxyribonucleic acid, is the chemical substance which makes up the genes and chromosomes of living organisms. It contains the code or set of instructions which guides the development, maintenance and reproduction of organisms and determines their form.

7. With the use of enzymes called restriction enzymes, or endonucleases, it is possible to cleave the DNA of one organism and splice in a portion of the DNA of a second organism which has been similarly cleaved. The splicing can be sealed with another enzyme called DNA ligase, and the composite DNA can then be inserted into a host organism where the foreign genetic information may be expressed and reproduced.

8. Using recombinant DNA techniques, genetic information from any living organism can be implanted into bacteria. Also, genetic information from lower organisms such as viruses can be inserted into and expressed in higher organisms. This rapid exchange of genetic information across wide species barriers, as can occur in recombinant DNA research, is rare in nature and limited by reproductive barriers.

9. The recombinant DNA technique is a powerful new scientific tool which, while providing speed and convenience in the conduct of genetic research, permits hitherto impossible genetic manipulations with little control over the outcome of these manipulations. It is now possible artificially to manipulate the course of evolution within a short period of time using a technique different and far more extensive than that of traditional breeding techniques. Recombinant DNA research raises unprecedented hazards to humans and the environment compounded by the inability to predict the outcome of the research, and the ability of a dangerous organism to replicate, maintain and establish itself in the ecosphere.

10. Escherichia coli (E. coli), the host organism most widely used in recombinant DNA research, is a ubiquitous organism which resides in the human gut, in all warm blooded species, economically important and otherwise, in water supplies, and other places. It has pathogenic, or disease causing capabilities. E. coli is frequently associated with upper urinary tract infections in humans. It is capable of transferring the foreign

DNA implanted in it to other microorganisms, which could result in the formation of a novel pathogen.

B. ENVIRONMENTAL IMPACTS OF RECOMBINANT DNA ACTIVITIES.

11. A number of hypothetical results have been suggested as possibly coming from recombinant DNA research. Whether these results can be realized is speculative and they may cause adverse environmental impacts or be accompanied by other deleterious effects.

A. The least uncertain result posed may be an increased knowledge of basic biologic processes and an understanding of some disease states.

B. Another hypothetical result may be improved food production through the endowment of plants with new synthesis capabilities such as increased photosynthetic fixation of carbon dioxide and nitrogen fixation by species unable to do so presently, such as cereals.

C. Another hypothetical result may be the synthesis of proteins, such as insulin, and other substances which may have medical or industrial applications.

D. The most speculative result posed is the possibility of finding cures for the many forms of cancer.

12. Each of the hypothetical results may be realizable through a number of alternative methods which may be safer, less hazardous to the environment and provide more realistic solutions to the problems being attacked.

A. Alternative methods in the search for biologic knowledge include traditional techniques or newer techniques, such as DNA synthesis, in which far greater experimental control is possible. Another possibility is that certain types of knowledge sought may create too great an opportunity for malevolent uses, thus suggesting that this line of research not be pursued.

B. Alternative methods for improving food supplies

include elimination of food deterioration and waste, improved distribution of current food supplies, improved agricultural education and population stabilization.

C. Alternative methods of increasing the supply of insulin include the increased production of swine to provide a greater volume of swine pancreas for the manufacture of insulin, further research into the protein synthesis of insulin or its production using tissue culture methods. Alternative therapies for treating diseases such as diabetes may also be developed.

D. Alternative methods of seeking cures for cancer include the identification and removal of carcinogens from the environment and research using other techniques.

13. Just as there are hypothetical results which could come from recombinant DNA research, there are also risks and potential hazards. For example, it is possible to stitch in genes which are toxigenic or pathogenic or which confer drug resistance.

A. The risk and potential hazard of most immediate concern is the use of organisms in recombinant DNA research which are ubiquitous and/or dangerous to humans, plants or animals. E. coli, which is discussed in Paragraph 10 above, could cause serious health problems if a dangerous gene were implanted and the organism escaped the laboratory and survived or passed along the dangerous genetic component. The hazards of working with other organisms can be similar and each warrants individual experimental examination in order to assess the hazards. The dangers extend from laboratory workers to the public at large, to plant and animal species, to the equilibrium of the ecosphere as a whole.

B. Recombinant DNA research creates the risk of theft of dangerous new organisms or sabotage by terrorists,

criminals, psychopaths or extortionists.

C. Recombinant DNA research provides new opportunities for germ warfare research with its dangerous implications.

D. Recombinant DNA research creates the risk and potential hazard of new diseases in man, animals and crops, and possible dangers to forests, rangeland, wildlife, and fisheries.

C. ACTIONS AND DETERMINATIONS OF DEFENDANTS WITH RESPECT TO RECOMBINANT DNA RESEARCH.

14. Upon information and belief the National Institutes of Health (NIH) provided much of the funding for the scientific investigations leading to the development of recombinant DNA techniques by making research grants under authority of the Public Health Service Act, 42 U.S.C.§241 and 2421.

15. The NIH has continued to fund research using recombinant DNA techniques under the same authority as stated in Paragraph 14 herein. The grant awards for projects which involve some aspect of recombinant DNA research amounted to approximately $12 million as of the end of February, 1977. Many of these grant awards will continue for a period of several years.

16. As of mid-March, 1977, the NIH had 123 grants in which recombinant DNA research is involved.

17. As of mid-February, 1977, the NIH had more than 10 on-going intramural recombinant DNA research projects being conducted within the agency.

18. Upon information and belief the NIH is setting up high containment laboratories at its facilities in Bethesda, Maryland and at Fort Detrick in Frederick, Maryland, for the purpose of conducting recombinant DNA research.

19. Upon information and belief the NIH has let contracts for the construction and/or renovation of laboratories for the conduct of recombinant DNA research at Harvard University, the

University of Michigan, and the Albert Einstein Medical Center of Yeshiva University.

20. On October 7, 1974 the Secretary of Health, Education, and Welfare under authority of the Federal Advisory Committee Act, 5 U.S.C. App. I, and the Public Health Service Act, 42 U.S.C. §217a, chartered the Recombinant DNA Molecule Program Advisory Committee for the purpose of advising the Secretary of the Department of Health, Education, and Welfare, the Assistant Secretary for Health of the Department of Health, Education, and Welfare, the Director of NIH with respect to recombinant DNA research. On September 24, 1976 this Advisory Committee was renewed by the Secretary of the Department of Health, Education, and Welfare until June 30, 1978.

21. On June 23, 1976, the Director of NIH, with the approval of the Secretary of the Department of Health, Education, and Welfare (DHEW), and the Assistant Secretary for Health of the DHEW, promulgated guidelines for the conduct of recombinant DNA research being done by NIH grantees and by NIH personnel, entitled "Recombinant DNA Research Guidelines."

22. In or about June, 1976, the "Office of Recombinant DNA Activities" (ORDA) was established by the NIH. ORDA is responsible for keeping the Office of the Director of NIH informed of activities, research, and developments in the field of recombinant DNA research, and it is involved in all major planning activities leading to the formation of NIH policies and procedures with respect to recombinant DNA research.

23. On August 26, 1976, the Director of NIH issued a Draft Environmental Impact Statement (EIS) for the Recombinant DNA Research Guidelines. This Draft EIS was published in the Federal Register on September 9, 1976, 41 Fed. Reg. 38426.

D. REQUIREMENTS OF THE NATIONAL ENVIRONMENTAL POLICY ACT.

24. On January 1, 1970, the President of the United States

signed NEPA. It became effective immediately.

25. The purposes of NEPA include, among other things, "to declare a national policy which will encourage productive and enjoyable harmony between man and his environment; to promote efforts which will prevent or eliminate damage to the environment and biosphere and stimulate the health and welfare of man; to enrich the understanding of ecological systems and natural resources important to the Nation." NEPA §2.

26. Sections 101, 102 and 103 of NEPA provide as follows:

> §101(b). "In order to carry out the policy set forth in this chapter, it is the continuing responsibility of the Federal Government to use all practicable means, consistent with other essential considerations of national policy, to improve and coordinate Federal plans, functions, programs, and resources to the end that the Nation may--
>
> (1) fulfill the responsibilities of each generation as trustee of the environment for succeeding generations;
>
> (2) assure for all Americans safe, healthful, productive, and esthetically and culturally pleasing surroundings;
>
> (3) attain the widest range of beneficial uses of the environment without degradation, risk to health or safety, or other undesirable and unintended consequences;
>
> * * *
>
> §101(c). "The Congress recognizes that each person should enjoy a healthful environment and that each person has a responsibility to contribute to the preservation and enhancement of the environment.
>
> §102. "The Congress authorizes and directs that, to the fullest extent possible: (1) the policies, regulations, and public laws of the United States shall be interpreted and administered in accordance with the policies set forth in this chapter, and (2) all agencies of the Federal Government shall--
>
> (A) utilize a systematic, interdisciplinary approach which will insure the integrated use of the natural and social sciences and the environmental design arts in planning and in decisionmaking which may have an impact on man's environment;
>
> (B) identify and develop methods and procedures, in consultation with the Council on Environmental Quality established by subchapter II of this chapter, which

will insure that presently unquantified environmental amenities and values may be given appropriate consideration in decisionmaking along with economic and technical considerations;

(C) include in every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment, a detailed statement by the responsible official on--

(i) the environmental impact of the proposed action,

(ii) any adverse environmental effects which cannot be avoided should the proposal be implemented,

(iii) alternatives to the proposed action,

(iv) the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity, and

(v) any irreversible and irretrievable commitments of resources which would be involved in the proposed action should it be implemented.

Prior to making any detailed statement, the responsible Federal official shall consult with and obtain the comments of any Federal agency which has jurisdiction by law or special expertise with respect to any environmental impact involved. Copies of such statement and the comments and views of the appropriate Federal, State, and local agencies, which are authorized to develop and enforce environmental standards, shall be made available to the President, the Council on Environmental Quality and to the public as provided by section 552 of Title 5, and shall accompany the proposal through the existing agency review processes;

* * *

(E) study, develop, and describe appropriate alternatives to recommended courses of action in any proposal which involves unresolved conflicts concerning alternative uses of available resources;

(F) recognize the worldwide and long-range character of environmental problems and, where consistent with the foreign policy of the United States, lend appropriate support to initiatives, resolutions, and programs designed to maximize international cooperation in anticipating and preventing a decline in the quality of mankind's world environment;

(G) make available to States, counties, municipalities, institutions, and individuals, advice and information useful in restoring, maintaining, and enhancing the quality of the environment;

(H) initiate and utilize ecological information in the planning and development of resource-oriented projects; and

(I) assist the Council on Environmental Quality established by subchapter II of this chapter."

§103. "All agencies of the Federal Government shall review their present statutory authority, administrative regulations, and current policies and procedures for the purpose of determining whether there are any deficiencies or inconsistencies therein which prohibit full compliance with the purposes and provisions of this chapter and shall propose to the President not later than July 1, 1971, such measures as may be necessary to bring their authority and policies into conformity with the intent, purposes, and procedures set forth in this chapter."

27. On or about March 5, 1970, the President of the United States promulgated Executive Order 11514, 35 Fed. Reg. 4247, entitled "Protection and Enhancement of Environmental Quality," directing the heads of all Federal agencies to proceed with all actions required by §102 of NEPA and to:

"(d) Review their agencies' statutory authority, administrative regulations, policies, and procedures, including those relating to loans, grants, contracts, leases, licenses, or permits, in order to identify any deficiences or inconsistencies therein which prohibit or limit full compliance with the purposes and provisions of the Act."

28. Executive Order 11514 also directed the Council on Environmental Quality to:

"(h) Issue guidelines to Federal agencies for the preparation of detailed statements on proposals for legislation and other Federal actions affecting the environment, as required by section 102(2)(C) of the Act."

29. In or about August, 1973, the Council on Environmental Quality issued revised guidelines (hereinafter "CEQ Guidelines") for preparing detailed environmental statements as required by section 102(2)(C) of NEPA, entitled "Preparation of Environmental Impact Statements: Guidelines," 38 Fed. Reg. 20550, 40 C.F.R. Part 1500. The CEQ Guidelines further provides that

§1500.1(a) "....Underlying the preparation of such environmental statements is the mandate of both the Act and Executive Order 11514 (35 FR 4247) of March 5, 1970 (3 CFR, 1966-70 Comp., p.902), that all Federal Agencies, to the fullest extent possible,

direct their policies, plans and programs to protect and enhance environmental quality....."

30. The CEQ Guidelines further provides that

§1500.2(a). "As early as possible and in all cases prior to agency decision concerning recommendations or favorable reports on proposals for (1) legislation significantly affecting the quality of the human environment (see §§ 1500.5(i) and 1500.12)(hereafter "legislative actions") and (2) all other major Federal actions significantly affecting the quality of the human environment (hereafter "administrative actions"), Federal agencies will, in consultation with other appropriate Federal, State and local agencies and the public assess in detail the potential environmental impact."

31. The CEQ Guidelines further provides that

§1500.3(a). "....Each agency, including both departmental and subdepartmental components having such procedures, shall review its procedures and shall revise them, in consultation with the Council, as may be necessary in order to respond to requirements imposed by these revised guidelines as well as by such previous directives....."

32. On or about October 17, 1973, pursuant to NEPA, Executive Order 11514 and the CEQ Guidelines, the Department of Health, Education, and Welfare promulgated its procedures for compliance with NEPA in the DHEW General Administration Manual (GAM), Part 30. The DHEW GAM, Part 30 provides, among other things, that

"30-10-50 GENERAL DEPARTMENTAL POLICY

A. Introduction. This section sets forth the general policy of the Department regarding the implementation of NEPA. All activities of the Department subject to NEPA and the regulations published under that authority are to be carried out in accordance with policies of this chapter.

B. Actions Having Impact on the Environment. NEPA requires that the environmental impact of all federal actions be fully assessed before the decision to take the action is made. The Department hereby establishes the following general policies in order to effectively implement the requirements and spirit of the Act.

* * *

C. Applicability. The procedures set forth in

Chapter 30-11 and 30-12 are to be followed with regard to all Departmental actions, including research activities, that have reached a state of investment or commitment likely to determine subsequent development or to restrict later alternatives. When possible, the environmental effects of a series of actions should be reviewed collectively since the effect of many federal decisions concerning a project or complex of projects can be individually limited but collectively considerable. Departmental actions are defined as:

1. Approving any application for federal assistance (including loans, guarantees and grants);

2. Recommending or reporting favorably on any legislation (including extensions of existing authorities and appropriations) which would be the responsibility of this Department;

3. Committing federal funds to any Department-initiated activity;

4. Granting, approving, modifying, or cancelling any federal contract or any federal license, permit, easement, certificate, or other entitlement for use, manufacture or sale;

5. Approving, amending, or revoking any policy, procedure, or regulation, including the establishment of the Department's programs;

6. Proposing any agency budget; and

7. Recommending the adoption of any Policy Development and Implementation Plan (PDI)."

* * *

"30-11-00 INTRODUCTION

Each Direct-Reporting Officer shall review or coordinate a review of the programs and/or typical classes of actions in his area of responsibility to determine whether the programs or activities could, under ordinary circumstances, support individual actions that would have a significant environmental impact, thus, requiring the development of an Environmental Impact Statement. The review shall result in either a Statement of Inapplicability or the development of Environmental Guidelines. In addition, the review may determine the need to develop an Environmental Impact Statement for the program/class of actions as a whole."

* * *

"30-12-00 INTRODUCTION

> Actions which are part of a program (or group of activities) that do not have a Statement of Inapplicability (Chapter 30-11-20) to the NEPA requirements, must be reviewed on an individual basis to determine the extent of the effects the action would have on the environment. This This Chapter discusses the necessary review and documentation for individual actions."

E. FAILURE TO COMPLY WITH THE NATIONAL ENVIRONMENTAL POLICY ACT.

33. The NIH has developed a full program for the purpose of pursuing recombinant DNA research. It has created the Recombinant DNA Molecule Program Advisory Committee, established the Office of Recombinant DNA Activities, and promulgated Guidelines for the conduct of this research. It has funded, is funding, and intends to continue funding recombinant DNA research into the future. It has let contracts for the construction and/or renovation of laboratories for recombinant DNA research, and is setting up its own laboratories for this research.

34. The recombinant DNA research program of the NIH and each of the actions described above in Paragraphs 14 through 23 and 33, has and will have profound short and long term effects upon the quality of the human environment and upon the maintenance of a productive and enjoyable harmony between man and his environment and will have profound effects on the health and welfare of present and future generations over the entire planet.

35. In the conception and development of the recombinant DNA research program, including the funding of research projects and laboratory construction, and the promulgation of the Recombinant DNA Research Guidelines, defendants have violated and disregarded the decisionmaking processes required by NEPA, Executive Order 11514, the CEQ Guidelines, the DHEW GAM, and other provisions of law, in that defendants, among other things, have:

A. Refused and failed to prepare final environmental impact statements which detail alternatives and other matters required by NEPA, the CEQ Guidelines, and the DHEW GAM, before taking action with respect to

(i) the recombinant DNA research program as a whole;

(ii) each grant funded by NIH for the purpose of conducting recombinant DNA research;

(iii) each recombinant DNA research project conducted within the NIH;

(iv) each contract let for the construction and/or renovation of facilities for the conduct of recombinant DNA research;

(v) the construction and/or renovation of NIH facilities for the conduct of recombinant DNA research;

(vi) the promulgation of the Recombinant DNA Research Guidelines;

each of which constitutes a major Federal action significantly affecting the quality of the human environment;

B. Failed and omitted to study, develop and describe appropriate alternatives to the recombinant DNA research program and each recombinant DNA research project, including, among others, those alternatives set out in Paragraph 12;

C. Failed, as part of the decisionmaking process, to assess the alleged economic and technical benefits against the environmental costs;

D. Failed to utilize a systematic, interdisciplinary approach which will insure the integrated use of the natural and social sciences and the environmental design arts in planning and decisionmaking which may have an impact on man's environment;

E. Failed to identify and develop methods and procedures, in consultation with the Council on Environmental Quality, which will insure that presently unquan-

tified environmental amenities and values may be given appropriate consideration in decisionmaking along with economic and technical considerations;

F. Failed to recognize the worldwide and long-range character of environmental problems associated with recombinant DNA research;

G. Failed to initiate and utilize ecological information in the planning and development of the recombinant DNA research program, the Recombinant DNA Research Guidelines, and each recombinant DNA research project;

H. Acted arbitrarily and capriciously and in violation of Sections 2, 101 and 102 of NEPA by not assessing the recombinant DNA research program and the Recombinant DNA Research Guidelines in comparison with the alternatives to that program and the Guidelines, and, on the basis of that assessment, adopting that course which most conforms with NEPA's objectives;

I. Failed to bring the authority and policies of the NIH into conformity with the intent, purposes, and procedures set forth in NEPA, the CEQ Guidelines, and the DHEW GAM, as required by Section 103 of NEPA, Executive Order 11514 and the CEQ Guidelines.

36. Despite the illegality of defendants' actions described above, defendants have:

A. Continued to permit NIH grantees and personnel to engage in recombinant DNA research;

B. Implemented and applied the Recombinant DNA Research Guidelines;

C. Let contracts to Harvard University, the University of Michigan, and the Albert Einstein Medical Center of Yeshiva University, among other places, for the purpose of constructing and/or renovating laboratories for the

conduct of recombinant DNA research;

D. are setting up laboratories at NIH facilities for the purpose of conducting recombinant DNA research.

37. Plaintiff has no adequate remedy at law.

IV. AS AND FOR PLAINTIFF'S SECOND CLAIM

38. Plaintiff repeats and realleges each and every allegation set forth in Paragraphs 1 through 37 with the same effect as though herein fully set forth.

39. In taking the actions of

(i) developing and pursuing the recombinant DNA research program;

(ii) funding research projects and construction and/or renovation of facilities for the purpose of conducting recombinant DNA research; and

(iii) promulgating the Recombinant DNA Research Guidelines;

defendants have not, to the fullest extent possible, executed and administered the policies, regulations and public laws with the execution and administration of which they are charged, in accordance with the policies set forth in NEPA, and the said actions are, accordingly, arbitrary.

40. Plaintiff has no adequate remedy at law.

V. AS AND FOR PLAINTIFF'S THIRD CLAIM

41. Plaintiff repeats and realleges each and every allegation set forth in Paragraphs 1 through 40 with the same effect as though herein fully set forth.

42. In or about September, 1976, the Secretary of DHEW, with the approval of the President of the United States, convened the "Interagency Committee on Recombinant DNA Research." Dr. Donald S. Fredrickson, Director of the NIH and a defendant herein, serves as chairman of this Committee at the request of the Secretary of DHEW.

43. The mandate of the Committee, as stated in its Interim Report, dated March 15, 1977, is to

> "(1) review the nature and seope of Federal- and private-sector activities relating to recombinant DNA research;
>
> (2) determine the extent to which the NIH Guidelines may currently be applied to research in the public and private sectors;
>
> (3) recommend, if appropriate, legislative or executive actions necessary to ensure compliance with the standards set for this research; and
>
> (4) provide for the full communication and necessary exchange of information on recombinant-DNA-research programs and activities throughout the Federal sector."

44. The Interagency Committee, in its Interim Report, dated March 15, 1977, made proposals to the Secretary of DHEW for recommended legislation.

45. Proposed legislation incorporating these recommendations was drafted by the Department of Health, Education, and Welfare, entitled "A Bill to regulate activities involving recombinant deoxyribonucleic acid," and transmitted to the Congress of the United States by Joseph A. Califano, Jr., Secretary of the DHEW and a defendant herein, on April 4, 1977.

46. The proposed legislation initially incorporates the NIH Recombinant DNA Research Guidelines, and in addition has

many other provisions relating to recombinant DNA activities.

47. The CEQ Guidelines provides that:

"§1500.5 Types of action covered by the Act.

(a) "Actions" include but are not limited to:

(1) Recommendations or favorable reports relating to legislations including requests for appropriations. The requirement for following the section 102(2)(C) procedures as elaborated in these guidelines applies to both (i) agency recommendations on their own proposals for legislation (see §1500.12); and (ii) agency reports on legislation initiated elsewhere. In the latter case only the agency which has primary responsibility for the subject matter involved will prepare an environmental statement."

* * *

"§1500.12 Legislative actions.

(b) With respect to recommendations or reports on proposals for legislation to which section 102(2)(C) applies, the final text of the environmental statement and comments thereon should be available to the Congress and to the public for consideration in connection with the proposed legislation or report. In cases where the scheduling of congressional hearings on recommendations or reports on proposals for legislation which the Federal agency has forwarded to the Congress does not allow adequate time for the completion of a final text of an environmental statement (together with comments), a draft environmental statement may be furnished to the Congress and made available to the public pending transmittal of the comments as received and the final text."

48. The DHEW GAM, Part 30, provides that:

"30-13-20 POLICY FOR NEPA COMPLIANCE ON LEGISLATIVE ITEMS: An Environmental Statement Shall Accompany Legislative Items Proposing Significant Environmental Effects.

Except as provided by 30-13-60A, no officer or employee of the Department shall approve or recommend favorable action on behalf of a division, office, bureau, administration, institute, or service of the Department, of a legislation for which, if enacted, the Department would have primary responsibility and which, under the guidelines established by the Department amplifying or implementing the

Council on Environmental Quality (CEQ) Guidelines, 38 FR 20550 (August 1, 1973), promulgated by the Secretary or any of the officers named in 30-13-30A would significantly affect the environment unless the legislative item is accompanied by an environmental statement pertaining thereto that conforms to §1500.8 of the CEQ Guidelines, as amplified or implemented by Department guidelines."

* * *

"30-13-60 MODIFICATION AND WAIVERS

A. Assistant General Counsel for Legislation May Modify or Waive Application of Regulation for Good Cause in Particular Cases."

* * *

49. Neither a draft EIS or a final EIS was prepared by the defendants or any of them on the proposed legislation set forth in Paragraph 45.

50. The proposed legislation set forth in Paragraph 45 has and will have profound short and long-term effects upon the quality of the human environment and upon the maintenance of a productive and enjoyable harmony between man and his environment and will have profound effects on the health and welfare of present and future generations over the entire planet.

51. There is no good cause for failing to prepare an environmental impact statement on the part of the defendants.

52. In the conception and development of the proposed legislation referred to in Paragraph 45 and its transmittal to Congress, the defendants have violated and disregarded the decisionmaking processes required by NEPA, Executive Order 11514, the CEQ Guidelines and the DHEW GAM, in that defendants, among other things, have failed to prepare a detailed statement of environmental impacts, alternatives and other matters required by NEPA with respect to this proposed legislation, which constitutes a major Federal action significantly affecting the quality of the human environment.

53. Despite the illegality of defendants' actions in connection with the legislation described above, defendants have transmitted this proposed legislation to the Congress.

54. Plaintiff has no adequate remedy at law.

VI. AS AND FOR PLAINTIFF'S FOURTH CLAIM

55. Plaintiff repeats and realleges each and every allegation set forth in Paragraphs 1 through 37 with the same effect as though herein fully set forth and repeated.

56. Defendants are authorized to promulgate regulations governing NIH funded research by the Public Health Service Act, 42 U.S.C. §§216(b) and 242(m)(b)(1).

57. Subsection 4 of section 2 of the Administrative Procedure Act, 5 U.S.C. §551(4), provides:

> "'rule' means the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency and includes the approval or prescription for the future of rates, wages, corporate or financial structures or reorganizations thereof, prices, facilities, appliances, services or allowances therefor or of valuations costs, or accounting, or practices bearing on any of the foregoing;"

58. Subsection 5 of section 2 of the Administrative Procedure Act, 5 U.S.C. §551(5), provides:

> "'rule making' means agency process for formulating, amending, or repealing a rule;"

59. Section 4 of the Administrative Procedure Act, 5 U.S.C. §553, provides:

> "(a) This section applies, according to the provisions thereof, except to the extent that there is involved -
> (1) a military or foreign affairs function of the United States; or
> (2) a matter relating to agency management or personnel or to public property, loans, grants, benefits, or contracts.
>
> "(b) General notice of proposed rule making shall be published in the Federal Register, unless persons subject therto are named and either personally served or otherwise have actual notice thereof in accordance with law. The notice shall include -
> (1) a statement of the time, place, and nature of public rule making proceedings;
> (2) reference to the legal authority under which the rule is proposed; and
> (3) either the terms or substance of the proposed rule or a description of the subjects and issues involved.

Except when notice or hearing is required by statute, this subsection does not apply -

(A) to interpretative rules, general statements of policy, or rules of agency organization, procedure, or practice; or

(B) when the agency for good cause finds (and incorporates the finding and a brief statement of reasons therefor in the rules issued) that notice and public procedure thereon are impractible, unnecessary, or contrary to the public interest.

"(c) After notice required by this section, the agency shall give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments with or without opportunity for oral presentation. After consideration of the relevant matter presented, the agency shall incorporate in the rules adopted a concise general statement of their basis and purpose. When rules are required by statute to be made on the record after opportunity for an agency hearing, sections 556 and 557 of this title apply instead of this subsection.

"(d) The required publication or service of a substantive rule shall be made not less than 30 days before its effective date, except -

(1) a substantive rule which grants or recognizes an exemption or relieves a restriction;

(2) interpretative rules and statements of policy; or

(3) as otherwise provided by the agency for good cause found and published with the rule.

"(e) Each agency shall give an interested person the right to petition for the issuance, amendment, or repeal of a rule."

60. The Recombinant DNA Molecule Program Advisory Committee established by DHEW and NIH held meetings on February 28, 1975, May 12-13, 1975, July 18-19, 1975, December 4-5, 1975, and April 1-2, 1976, during which meetings guidelines for the conduct of recombinant DNA research were drafted and discussed. Notice and announcement of the meeting of said Committee were made in the Federal Register.

61. The purpose for the February 28, 1975 meeting of said Committee as stated in the Federal Register was:

"to discuss: the role of the committee, the status of research in the field, research studies required, the mechanisms by which such studies should be supported, and the

identification of facilities and resources needed for their performance." 40 Fed. Reg. 3488, January 22, 1975.

62. The purpose for the May 12-13, 1975 meeting of said Committee as stated in the Federal Register was:

> "to discuss: the status of research in the field, research studies required, the mechanisms by which such studies should be supported, resources needed for their performance." 40 Fed. Reg. 14965, April 3, 1975.

63. The purpose for the July 18-19, 1975 meeting of said Committee as stated in the Federal Register was:

> "to discuss: the status of research in the field, research studies required, the mechanisms by which such studies should be supported, and the identification of facilities and resources needed for their performance." 40 Fed. Reg. 24764, June 10, 1975.

64. The purpose for the December 4-5, 1975 meeting of said Committee as stated in the Federal Register was:

> "to discuss: guidelines for research involving recombinant DNA molecules, the status of research in the field, research studies required, the mechanisms by which such studies should be supported, and the identification of facilities and resources needed in their performance." 40 Fed. Reg. 46392, October 7, 1975.

65. The purpose of the April 1-2, 1976 meeting of the said Committee as stated in the Federal Register was:

> "to discuss: guidelines for research involving recombinant DNA molecules, the status of research in the field, research studies required, the mechanisms by which such studies should be supported, and the identification of facilities and resources needed in their performance." 41 Fed. Reg. 6307, February 12, 1976.

66. Proposed guidelines for recombinant DNA research were also considered at a meeting of the Advisory Committee to the Director of NIH, held on February 9-10, 1976. Notice of this meeting in the Federal Register statedthat the purpose of the meeting was to

> "consider proposed guidelines and requirements concerning recombinant DNA molecule research

conducted and supported by the NIH, and other policy issues of concern to the Director, NIH." 41 Fed. Reg. 2105, January 14, 1976.

67. The notices of the meetings of the Recombinant DNA Molecule Program Advisory Committee and the Advisory Committee to the Director of the NIH, as set forth in the preceding Paragraphs 61 through 66, do not constitute the "general notice of proposed rule making" as required by subsection (b) of section 4 of the APA, 5 U.S.C. §553(b). The aforesaid notices fail to indicate that a rulemaking proceeding is to take place. They fail to make reference to the legal authority under which the rule is proposed. And they fail to set forth either the substance or terms of the proposed rules or a description of the subjects and issues involved.

68. The aforesaid notices are not calculated to elicit comment for a rulemaking proceeding and are inadequate.

69. The proposed guidelines were not published in the Federal Register in order to make them available for public scrutiny and give the public adequate opportunity for participation.

70. Public hearings were held neither on the proposed guidelines as a whole, nor on the many controversial factual issues concerning the guidelines, matters of great public concern and controversy and having an enormous impact on the human environment and the entire ecosphere.

71. On June 23, 1976, Donald S. Fredrickson, Director of NIH, with the concurrence of the Secretary of DHEW, and the Assistant Secretary for Health of DHEW, who are the defendants herein, promulgated the Recombinant DNA Research Guidelines which govern the conduct of NIH supported research using recombinant DNA techniques.

72. The said Guidelines, as promulgated, were effective immediately upon release, on June 23, 1976.

73. On July 7, 1976, the said Guidelines, and the decision of the Director of the NIH concerning the promulgation of the Guidelines, were published in the Federal Register, 14 days after they had become effective. Neither the final version of the Guidelines or any earlier version had been previously published in the Federal Register.

74. The said Guidelines, as promulgated, set forth detailed rules categorizing experiments, determining which types of experiments are prohibited, and for those permitted, the conditions under which they may be performed. See, 41 Fed. Reg. 27914-20, July 7, 1976.

75. The said Guidelines, as promulgated, create an administrative framework, assigning roles and responsibilities for the governing of recombinant DNA research to (1) the principal investigator, (2) institutional biohazards committees in institutions where the research is to be conducted, (3) NIH Initial Review Groups (Study Sections), (4) the NIH Recombinant DNA Molecule Program Advisory Committee, and (5) the NIH staff. See, 41 Fed. Reg. 27920-21, July 7, 1976.

76. The said Guidelines, as promulgated, set forth the following responsibilities of the NIH staff:

> "(i) Assuring that no NIH grants or contracts are awarded for DNA recombinant research unless they (a) conform to these guidelines, (b) have been properly reviewed and recommended for approval, and (c) include a properly executed Memorandum of Understanding and Agreement,.....
>
> (iii) receiving and reviewing applications for approval to lower containment levels when a cloned DNA recombinant derived from a shotgun experiment has been rigorously characterized and there is sufficient evidence that it is free of harmful genes,.....
>
> and (v) performing site inspections of all P4 physical containment facilities, engaged in DNA recombinant research, and of other facilities as deemed necessary."
> 41 Fed. Reg. 27921, July 7, 1976.

77. If a grantee fails to abide by said Guidelines, as promulgated, he/she is subject to various sanctions. §52.26 of the Public Health Service Regulations, 42 CFR §52.26, provides that

> "The Secretary may with respect to any grant award or class of awards impose additional conditions prior to or at the time of any award when in his judgment such conditions are necessary to assure or protect advancement of the approved project, the interests of the public health, or the conservation of grant funds." 28 Fed Reg. 10420, Sept. 26, 1963.

§52.11(a) of the Public Health Service Regulations, 42 CFR §52.11(a), provides for an exception to the general eligibility of persons for grants when

> "(3) Any individual, corporation, institution, agency or other such person who, having previously received a grant award has failed willfully and materially in the judgment of the Secretary to comply with accounting or other requirements applicable to such prior award, such disqualification to continue until terminated in the public interest by the Secretary." 28 Fed. Reg. 10420, Sept. 26, 1963, as amended at 33 Fed. Reg. 9821, July 9, 1968.

§74.112 of the regulations of the DHEW, 45 CFR §74.112, provides for termination of a grant when there is a violation of its terms and conditions:

> "When a grantee has materially failed to comply with the terms and conditions of a grant, the granting agency may suspend the grant, in accordance with §74.113, terminate the grant for cause, as provided in §74.114, or take such other remedies as may be legally available and appropriate in the circumstances."

78. The said Guidelines have the force of law, are "rules" within the meaning of the term as defined in the APA, and are subject to the rulemaking requirements of section 4 of the APA, 5 U.S.C. §553.

79. In the conception, development, and promulgation of the Recombinant DNA Research Guidelines, the defendants have violated and disregarded the decisionmaking processes required by section 4 of the APA, in that defendants have, among other

things

A. failed to publish general notice of proposed rule making in the Federal Register as required by subsection (b) of section 4 of the APA;

B. failed to comply with subsection (c) of section 4 of the APA by not providing an opportunity for comment on the rulemaking proceeding after giving proper notice that a rule making proceeding was indeed in progress;

C. failed to hold public hearings on the proposed guidelines or on controversial factual issues concerning the proposed guidelines, matters of the highest public importance and of enormous impact, and over which there has been much controversy;

D. failed to comply with subsection (d) of section 4 of the APA, by not publishing the Recombinant DNA Research Guidelines at least 30 days before their effective date.

80. The promulgation of the said Guidelines by defendants in disregard of the procedural requirements of the APA is ultra vires and illegal.

81. The failure of defendants to comply with the procedural requirements of the APA render the said Guidelines invalid and without force or effect.

82. Despite the illegality of defendants' actions in promulgating the Recombinant DNA Research Guidelines and the resulting invalidity of the Guidelines, defendants have implemented and continue to apply said Guidelines as though they had full force and effect.

83. The illegal actions of defendants in failing to comply with the requirements of the APA adversely affects the rights and interests of the plaintiff.

84. The plaintiff is without adequate remedy at law.

VII. AS AND FOR PLAINTIFF'S FIFTH CLAIM

85. Plaintiff repeats and realleges each and every allegation set forth in Paragraphs 1 through 40 and 55 through 84 with the same effect as though herein fully set forth and repeated.

86. The action of the defendants in developing and promulgating the Recombinant DNA Research Guidelines is arbitrary, capricious, an abuse of discretion, contrary to the provisions of the APA and NEPA, and otherwise not in accordance with law in that, among other things:

A. The Guidelines are based on unsupported assumptions and lack a basis in experimental evidence, scientific data, or an assessment of hazards and risks to health and the environment;

B. The Guidelines permit the use of E. coli as a host organism without having adequately determined the absence of danger in its use in recombinant DNA research;

C. The phylogenetic basis of assigning risk in the Guidelines is an unexplained assumption and fails to take into account the hazards to plants and animals.

D. There is no basis to conclude that the hypothetical results to be gained from recombinant DNA research outweigh the risks in performing this research.

87. Plaintiff has no adequate remedy at law.

VIII. AS AND FOR PLAINTIFF'S SIXTH CLAIM

88. Plaintiff repeats and realleges each and every allegation set forth in Paragraphs 1 through 40 and 55 through 87 with the same effect as though herein fully set forth and repeated.

89. Section 301 of the Public Health Service Act, (original version at P.L. 78-410, 58 Stat. 691) 42 U.S.C. §241, provides:

> "The Surgeon General shall conduct in the Service, and encourage, cooperate with, and render assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of, and promote the coordination of research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man, including water purification, sewage treatment, and pollution of lakes and streams. In carrying out the foregoing the Surgeon General is authorized to -
>
> ....(c) Make grants-in-aid to universities, hospitals, laboratories, and other public or private institutions, and to individuals for such research projects as are recommended by the National Advisory Health Council, or with respect to cancer, recommended by the National Cancer Advisory Board.....
>
> ....(h) Adopt, upon recommendation of the National Advisory Health Council, or, with respect to cancer, upon recommendation of the National Cancer Advisory Board,...., such additional means as he deems necessary or appropriate to carry out the purposes of this section."

90. Effective on June 25, 1966, Reorganization Plan No. 3 of 1966, 31 Fed. Reg. 8855, 80 Stat. 1610, provides:

> "Section 1. Transfer of functions.
> (a) Except as otherwise provided in subsection (b) of this section, there are hereby transferred to the Secretary of Health, Education, and Welfare (hereinafter referred to as the Secretary) all functions of the Public Health Service, of the Surgeon General of the Public Health Service, and of all other officers and employees of the Public Health Service, and all functions of all agencies of or in the Public Health Service.
> (b) This section shall not apply to the functions vested by law in any advisory council, board, or committee of or in the Public Health Service which is established by law or is required by law to be established.
>
> Section 2. Performance of transferred functions.

> The Secretary may from time to time make such provisions as he shall deem appropriate authorizing the performance of any of the functions transferred to him by the provisions of this reorganization plan by any officer, employee, or agency of the Public Health Service or of the Department of Health, Education, and Welfare."

91. Upon information and belief the authority vested in the Surgeon General by Section 301 of the Public Health Service Act has been redelegated to the Director of NIH in accordance with Reorganization Plan No. 3 of 1966.

92. Recombinant DNA research constitutes "research projects" within the meaning of that term as used in Section 301(c) of the Public Health Service Act.

93. The Recombinant DNA Research Guidelines constitute "such additional means as he [Director of NIH] deems necessary or appropriate to carry out the purposes of this section" within the meaning of that phrase as used in Section 301(h) of the Public Health Service Act.

94. In the funding of recombinant DNA research and in the development and promulgation of the Recombinant DNA Research Guidelines, the defendants have violated and disregarded the decisionmaking processes required by Section 301 of the Public Health Service Act, in that defendants have, among other things,

A. Upon information and belief, defendants have neither sought nor received from the National Advisory Health Council the recommendations required by subsections (c) and (h) of Section 301 of the Public Health Service Act, with respect to making grants-in-aid for recombinant DNA research and promulgating the Recombinant DNA Research Guidelines which govern the conduct of such research.

B. Upon information and belief, defendants have neither sought nor received from the National Cancer Advisory Board, the recommendations required by subsections (c) and (h) of section 301 of the Public Health Service Act,

with respect to making grants-in-aid for cancer research using recombinant DNA techniques, and with respect to the adoption of the Recombinant DNA Research Guidelines for cancer research using recombinant DNA techniques.

95. The funding of recombinant DNA research and promulgation of Recombinant DNA Research Guidelines by defendants in disregard of the procedural requirements of subsections (c) and (h) of Section 301 of the Public Health Service Act is ultra vires and illegal.

96. The failure of defendants to comply with the procedural requirements of the Public Health Service Act render the funding of grants for recombinant DNA research and the promulgation of the Recombinant DNA Research Guidelines invalid and without force or effect.

97. Despite the illegality of defendants' actions in funding grants for recombinant DNA research and in promulgating the said Guidelines, the defendants continue to fund such grants and have implemented and applied said Guidelines as though they had full force and effect.

98. The illegal actions of defendants in failing to comply with the requirements of the Public Health Service Act adversely affects the rights and interests of the plaintiff.

99. The plaintiff is without adequate remedy at law.

IX. AS AND FOR PLAINTIFF'S SEVENTH CLAIM

100. Plaintiff repeats and realleges each and every allegation set forth in Paragraphs 1 through 40 and 55 through 99 with the same effect as though herein fully set forth and repeated.

101. Section 5 of the Federal Advisory Committee Act, 5 U.S.C. App. I §5, provides

> "(b) In considering legislation establishing, or authorizing the establishment of any advisory committee, each standing committee of the Senate and of the House of Representatives shall determine, and report such determination to the Senate or to the House of Representatives, as the case may be, whether the functions of the proposed advisory committee are being or could be performed by one or more agencies or by an advisory committee already in existence, or by enlarging the mandate of an existing advisory committee. Any such legislation shall--
>
> (1) contain a clearly defined purpose for the advisory committee;
>
> (2) require the membership of the advisory committee to be fairly balanced in terms of the points of view represented and the functions to be performed by the advisory committee;
>
> (3) contain appropriate provisions to assure that the advice and recommendations of the advisory committee will not be inappropriately influenced by the appointing authority or by any special interest, but will instead be the result of the advisory committee's independent judgment;
>
> * * *
>
> (c) To the extent they are applicable, the guidelines set out in subsection (b) of this section shall be followed by the President, agency heads, or other Federal officials in creating an advisory committee."

102. On or about September 24, 1976, the Secretary of the Department of Health, Education, and Welfare, a defendant herein, approved the revised Charter of the Recombinant DNA Molecule Advisory Committee.

103. Upon information and belief the said Committee has sixteen members appointed by the defendants herein.

104. The membership of said Committee as presently constituted by the defendants is defective, insufficient and in violation of the standards and requirements of Section 5 of the Federal Advisory Committee Act, in that, among other things:

A. It is not fairly balanced in terms of the points of view represented or the functions to be performed;

B. It does not assure that the advice and recommendations of the Advisory Committee will not be inappropriately influenced by the appointing authority or by any special interest.

105. Plaintiff has no adequate remedy at law.

X. RELIEF REQUESTED

WHEREFORE, plaintiff prays for judgment

A. Declaring that the actions of the defendants in connection with the recombinant DNA research program, including the actions and determinations

(1) to implement the recombinant DNA research program;

(2) to conduct recombinant DNA research;

(3) to make grants to individuals and institutions for the purpose of conducting recombinant DNA research;

(4) to let contracts for the construction and/or renovation of facilities for the conduct of recombinant DNA research;

(5) to construct and/or renovate NIH facilities for the purpose of conducting recombinant DNA research;

(6) to promulgate Guidelines for the regulation of the recombinant DNA research;

(7) to propose legislation regulating recombinant DNA activities;

have been and are contrary to applicable law.

B. Declaring that the defendants are required by §102(2)(C) of NEPA to prepare and circulate for comment a detailed final environmental impact statement with respect to each of the actions and determinations stated above.

C. Declaring that the defendants are required by §553 of the APA to give notice of a public rulemaking proceeding, provide an opportunity for public comment, and hold public hearings with respect to the promulgation of guidelines for the regulation of recombinant DNA research, and that the procedures followed by the defendants in promulgating the Recombinant DNA Research Guidelines are contrary to these requirements and defective and insufficient as a matter of law.

D. Declaring that the promulgation of the Recombinant DNA Guidelines by the defendants was and is arbitrary, capricious, an abuse of discretion, contrary to the provisions of the APA

and NEPA, and otherwise not in accordance with law, and that said Guidelines are invalid, inapplicable and without force and effect.

E. Enjoining and restraining defendants from each and every of the actions and determinations in "A" above.

F. Granting an order directing defendants to suspend those grants and portions of grants which have been made for the purpose of conducting recombinant DNA research.

G. Enjoining and restraining the construction and/or renovation of facilities for the conduct of recombinant DNA research presently in progress or proposed.

H. Mandating the defendants to study and determine the environmental and health effects of the actions described above, and of each of them, and to develop alternatives thereto, as required by Sections 2, 101, and 102 of NEPA, and on the basis of that study and assessment, to adopt that course which most conforms to NEPA's policies.

I. Declaring that the authority and policies of the NIH are not in conformity with the intent, purposes, and procedures set forth in NEPA, the CEQ Guidelines, and the DHEW GAM.

J. Mandating that the defendants bring the authority and policies of the NIH into conformity with the intent, purposes, and procedures set forth in NEPA, the CEQ Guidelines, and DHEW GAM.

K. Declaring that in taking the actions and determinations set forth in "A" above, defendants have not, to the fullest extent possible, executed and administered the policies, regulations and public laws with the execution and administration of which they are charged, in accordance with the policies set forth in NEPA, and the said action are accordingly, arbitrary.

L. Declaring that the membership of the Recombinant DNA Molecule Program Advisory Committee is not fairly balanced,

independent an free from inappropriate influence as required by Section 5 of the Federal Advisory Committee Act and is constituted contrary to law.

M. Enjoining and restraining defendants from convening meetings of the above Advisory Committee as long as its membership is improperly constituted.

N. Declaring that all previous recommendations and certifications made by the above Advisory Committee are ultra vires and invalid.

O. Declaring that defendants are required by Section 301 of the Public Health Service Act to obtain the recommendation of the National Advisory Health Council and the National Cancer Advisory Board prior to adopting any means for carrying out the recombinant DNA research program.

P. Declaring that the defendants' failure to obtain the recommendations of the National Advisory Health Council and the National Cancer Advisory Board with respect to items (1) through (6) in "A" above, was and is contrary to law.

Q. Granting such interlocutory relief to plaintiff, pending final judgment in this action, as may be necessary to prevent irreparable injury pending final judgment herein;

R. Granting plaintiff reasonable attorneys' fees and the costs and disbursements of this action; and

S. Granting to plaintiff such other and further relief as to the Court seems just.

Dated: New York, New York
May 6, 1977

Richard M. Hartzman
RICHARD M. HARTZMAN
attorney for plaintiff

Friends of the Earth, Inc.
72 Jane Street
New York, New York 10014
212-675-5911
212-866-8146

VERIFICATION

RICHARD M. HARTZMAN, being duly sworn, deposes and says: That deponent has read the foregoing complaint and knows the contents thereof: and that the same is true to deponent's own knowledge, except that as to those matters therein stated to be alleged on information and belief, and that as to those matters deponent believes it to be true. The grounds of deponent's belief as to all matters not stated on deponent's knowledge are as follows: Reports of public statements which deponent believes to be true, information from public officials and officers of organizations knowlegeable of the facts, and matters of public record.

Richard M. Hartzman
RICHARD M. HARTZMAN

Sworn to before me this
6 th day of May, 1977.

Howard S Atkin
NOTARY PUBLIC

HOWARD S. ATKIN
Notary Public, State of New York
No. 31-4532625
Qualified in New York County
Commission Expires March 30, 1978

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TATE OF NEW YORK, COUNTY OF ss.:

e undersigned, an attorney admitted to practice in the courts of New York State,

☐ Corporate Attorney certifies that the within has been compared by the undersigned with the original and found to be a true and complete copy.

☐ Attorney's Verification shows: deponent is the attorney(s) of record for in the within action; deponent has read the foregoing and knows the contents thereof; the same is true to deponent's own knowledge, except as to the matters therein stated to be alleged on information and belief, and that as to those matters deponent believes it to be true. This verification is made by deponent and not by

The grounds of deponent's belief as to all matters not stated upon deponent's knowledge are as follows:

e undersigned affirms that the foregoing statements are true, under the penalties of perjury.

ated:

The name signed must be printed beneath

TATE OF NEW YORK, COUNTY OF ss.:

being duly sworn, deposes and says: deponent is

☐ Individual Verification the in the within action; deponent has read the foregoing and knows the contents thereof; the same is true to deponent's own knowledge, except as to the matters therein stated to be alleged on information and belief, and as to those matters deponent believes it to be true.

☐ Corporate Verification the of a corporation, in the within action; deponent has read the foregoing and knows the contents thereof; and the same is true to deponent's own knowledge, except as to the matters therein stated to be alleged upon information and belief, and as to those matters deponent believes it to be true. This verification is made by deponent because is a corporation and deponent is an officer thereof.

he grounds of deponent's belief as to all matters not stated upon deponent's knowledge are as follows:

worn to before me on 19

The name signed must be printed beneath

TATE OF NEW YORK, COUNTY OF ss.:

being duly sworn, deposes and says: deponent is not a party to the action,

over 18 years of age and resides at

☐ Affidavit of Service By Mail On 19 deponent served the within upon attorney(s) for in this action, at the address designated by said attorney(s) for that purpose by depositing a true copy of same enclosed in a post-paid properly addressed wrapper, in — a post office — official depository under the exclusive care and custody of the United States Postal Service within the State of New York.

☐ Affidavit of Personal Service On 19 at deponent served the within upon the herein, by delivering a true copy thereof to h personally. Deponent knew the person so served to be the person mentioned and described in said papers as the therein.

sworn to before me on 19

The name signed must be printed beneath

NOTICE OF ENTRY

Sir:-Please take notice that the within is a *(certified)* true copy of a
duly entered in the office of the clerk of the within named court on 19

Dated,

Yours, etc.,

Attorney for

Office and Post Office Address

To

Attorney(s) for

NOTICE OF SETTLEMENT

Sir:—Please take notice that an order

of which the within is a true copy will be presented for settlement to the Hon.

one of the judges of the within named Court, at

on the day of 19
at M.
Dated,

Yours, etc.,

Attorney for

Office and Post Office Address

To

Index No. Year 19

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

FRIENDS OF THE EARTH, INC.,

Plaintiff,

- against -

JOSEPH A. CALIFANO, JR., et al,

Defendants.

COMPLAINT

Richard M. Hartzman,

Attorney for plaintiff

Office and Post Office Address, Telephone

Friends of the Earth, Inc.
72 Jane Street
New York, New York 10014
212-675-5911, 212-866-8146

To

Attorney(s) for

Service of a copy of the within

is hereby admitted.

Dated,

.....

Attorney(s) for

GG:bmj
7-3078

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

FRIENDS OF THE EARTH, INC., Plaintiff,	:	
-v-	:	ANSWER
JOSEPH A. CALIFANO, JR., individually and as Secretary of the Department of Health, Education and Welfare; JAMES F. DICKSON, III, M.D., Individually and as Assistant Secretary for Health of the Department of Health, Education and Welfare; DR. DONALD S. FREDERICKSON, individually and as Director of the National Institutes of Health, and THE NATIONAL INSTITUES OF HEALTH, Defendants.	:	77 Civ. 2225 (VLB)

Defendants, by their attorney Robert B. Fiske, Jr., United States Attorney for the Southern District of New York answer the complaint herein as follows:

ANSWER TO PLAINTIFF'S FIRST CLAIM

1. Defendants admit the allegations contained in paragraphs 5 through 7, 15 and 17 through 23 of the complaint.

2. Deny each and every allegation contained in paragraphs 2, 12, 13 and 34 through 37 of the complaint.

3. Defendants neither admit nor deny the allegations of paragraphs 1 and 24 through 32 of the complaint, because these paragraphs recite conclusions of law rather than allegations of fact, to which no responsive pleading is required. Defendants respectfully refer the Court to the text of the statutes, regulations and guidelines cited by plaintiff, and cases decided thereunder for full statements of the applicable law.

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7-3078

4. Defendants lack knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 3 of the complaint.

5. Defendants admit the allegations of paragraph 4 of the complaint except allege that Dr. James F. Dickson was Acting Assistant Secretary for Health at the time the complaint was filed and is now Deputy Assistant Secretary for Health.

6. Defendants admit the allegations of paragraph 8 of the complaint except lack knowledge or information sufficient to form a belief as to truth or falsity of the the allegation that the rapid exchange of genetic information across wide species barriers, as can occur in recombinant DNA research, is rare in nature and limited by reproductive barriers.

7. Defendants deny the allegation of paragraph 9 of the complaint except admit that the recombinant DNA technique is a powerful new scientific tool in the conduct of genetic research.

8. Defendants deny the allegations of paragraph 10 of the complaint except admit that Escherichia coli (E. Coli) K-12 is a host organism frequently used in recombinant DNA research.

9. Defendants deny the allegations of paragraph 11 of the complaint, except admit that it has been suggested by members of the scientific community that recombinant DNA research may yield, among other benefits, increased knowledge of basic biological processes, an increased understanding of some diseases, improved food production, synthesis of proteins such as insulin and other substances of medical or industrial application, and cures for certain forms of cancer.

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10. Defendants deny the allegations of paragraph 13 of the complaint except admit (1) that it is theoretically possible that recomibinant DNA research, as well as many other activities of human beings, could provide new opportunities for germ warfare research and (2) that it is theoretically possible that recombinant DNA research, as well as many other activities of human beings, could create the risk of new diseases and dangers to man, wildlife and plantlife; defendants allege that they know of no instance where recomibinant DNA research has created any new disease or danger to man, wildlife or plantlife; defendants further allege that the theoretical dangers adverted to above have been minimized with respect to research funded by the National Institutes of Health by the promulgation by NIH of the Recombinant DNA Research Guidelines on June 23, 1976.

11. Deny the allegations of paragraph 14 of the complaint except admit that NIH funded scientific investigations leading to the development of recombinant DNA techniques by making grants pursuant to the Public Health Service Act, 42 U.S.C. §§ 241 and 242L.

12. Deny the allegations of paragraph 16 of the complaint except allege as of mid-July 1977, the NIH has funded approximately 180 grants in which recombinant DNA research is involved.

13. Deny the allegations of paragraph 33 of the complaint except admit that NIH established the Recombinant DNA Molecule Program Advisory Committee and the Office of Recombinant DNA Activities and promulgated guidelines governing the conduct of recombinant DNA research by recipients of NIH grants, and allege that NIH is funding and will fund in the future research involving recombinant DNA techniques only to the extent that such research is

conducted in accordance with the Recombinant DNA Research Guidelines and is of scientific merit, and only to the extent that monies are available for such funding.

ANSWER TO PLAINTIFF'S SECOND CLAIM

14. Defendants answer paragraph 38 by repeating defendants' responses to paragraphs 1 through 37 of the complaint.

15. Defendants deny each and every allegation contained in paragraphs 39 and 40 of the complaint.

ANSWER TO PLAINTIFF'S THIRD CLAIM

16. Defendants answer paragraph 41 by repeating defendants' responses to paragraphs 1 through 40 of the complaint.

17. Defendants admit the allegations contained in paragraphs 42 through 44 of the complaint.

18. Defendants deny each and every allegation contained in paragraphs 49 and 51 through 54 of the complaint.

19. Defendants neither admit nor deny the allegations contained in paragraphs 47 and 48 of the complaint since they contain only allegations of law to which no responsive pleading is required. Defendants respectfully refer the Court to the text of the statutes, regulations and guidelines cited by plaintiff, and to the cases decided thereunder for full statements of the applicable law.

20. Defendants admit the allegations of paragraph 45 of the complaint except allege that the Department of Health, Education and Welfare's legislative proposal did not incorporate all the recommendations of the Interagency Committee on Recombinant DNA Research.

21. Defendants admit the allegations of paragraph 46 of the complaint except allege that HEW's proposed legislation permits the Secretary of HEW to make such modification of the Guidelines as he deems necessary.

22. Defendants lack knowledge or information sufficient to form a belief as to the truth or falsity of the allegations of paragraph 50 of the complaint.

ANSWER TO PLAINTIFF'S FOURTH CLAIM

23. Defendants answer paragraph 55 by repeating defendants' responses to paragraphs 1 through 37 of the complaint.

24. Defendants admit the allegations contained in paragraphs 60 through 66, 71, 72 and 77 of the complaint.

25. Defendants deny each and every allegation contained in paragraphs 67 through 70, 78 through 84 of the complaint.

26. Defendants neither admit nor deny the allegations of paragraphs 56 through 59 of the complaint because those paragraphs contain only allegations of law rather than allegations of fact, to which no responsive pleading is required. Defendants respectfully refer the Court to the text of the statutes, regulations and guidelines cited by plaintiff, and cases decided thereunder for full statements of the applicable law.

27. Defendants admit the allegations of paragraph 73 of the complaint and allege that notice was published in the Federal Register on January 14, 1976 (41 F.R. 2105) stating that copies of the proposed guidelines were available from NIH on request.

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28. Defendants deny the allegations of paragraphs 74, 75 and 76 of the complaint except admit that the Guidelines were published at page 27902 of 41 Federal Register on July 7, 1976 to which the Court is respectfully referred for a complete and accurate statement of the contents thereof.

29. Defendants deny the allegations of paragraph 82 of the complaint except admit that defendants have implemented and continue to apply the Recombinant DNA Research Guidelines as though they have full force and effect.

ANSWER TO PLAINTIFF'S FIFTH CLAIM

30. Defendants answer paragraph 85 by repeating defendants' responses to paragraphs 1 through 40 and 55 through 84 of the complaint.

31. Defendants deny each and every allegation in paragraphs 86 and 87 of the complaint.

ANSWER TO PLAINTIFF'S SIXTH CLAIM

32. Defendants answer paragraph 88 by repeating defendants' responses to paragraphs 1 through 40 and 55 through 87 of the complaint.

33. Defendants admit the allegations contained in paragraphs 89 and 90 of the complaint.

34. Defendants deny each and every allegation contained in paragraphs 92 through 99 of the complaint.

35. Defendants deny each and every allegation contained in paragraph 91 of the complaint; and allege that pursuant to HEW Reorganization Plan No. 3 all functions of the Surgeon General were transferred to the Secretary of HEW, that certain of the aforementioned functions were delegated to the Assistant Secretary for Health, and that certain functions were in turn redelegated to the Director, NIH.

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ANSWER TO PLAINTIFF'S SEVENTH CLAIM

36. Defendants answer paragraph 100 by repeating defendants' responses to paragraphs 1 through 40 and 55 through 99 of the complaint.

37. Defendants admit the allegations of paragraph 102 of the complaint.

38. Defendants deny each and every allegation contained in paragraphs 104 and 105 of the complaint.

39. Defendants deny each and every allegation of paragraph 103 of the complaint and allege that as of June 13, 1977 the Recombinant DNA Molecule Committee had 14 members.

40. Defendants neither admit nor deny the allegations of paragraph 101 of the complaint because that paragraph contains only allegations of law rather than allegations of fact, to which no responsive pleading is required. Defendants respectfully refer the Court to the text of the statutes, regulations and guidelines cited by plaintiff, and cases decided thereunder for full statements of the applicable law.

AS A FIRST AFFIRMATIVE DEFENSE

41. The complaint fails to state a claim upon which relief can be granted.

AS A SECOND AFFIRMATIVE DEFENSE

42. Plaintiff lacks standing to assert the claims for relief set forth in the complaint under the Administrative Procedure Act, 5 U.S.C. §551 *et seq.*, the Public Health Service Act, 42 U.S.C. § 201 *et seq.*, and the Federal Advisory Committee Act, 5 U.S.C. App. I, and the regulations promulgated pursuant to the cited statutes.

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AS A THIRD AFFIRMATIVE DEFENSE

43. Plaintiff's assertion of claims purportedly arising out of past funding by defendants of research projects in which recombinant DNA techniques are used is barred by laches.

AS A FOURTH AFFIRMATIVE DEFENSE

44. Plaintiff has failed to join a number of indespensable parties to the action, to wit, each recipient of NIH grants that conducts research using the recombinant DNA technique and each person and each entity with contracts with defendants concerning the renovation or construction of facilities in which recombinant DNA research is presently in progress or is proposed.

WHEREFORE defendants respectfully request judgment dismissing the complaint, the award to defendants of their costs and disbursements, and such other relief as this Court deems proper.

Dated: New York, New York
July 8, 1977

Yours, etc.

ROBERT B. FISKE, JR.,

United States Attorney for the
Southern District of New York
Attorney for the Defendants

By: _____
FRANK WOHL
Assistant United States Attorney
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United States Courthouse Annex
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TO: RICHARD M. HARTZMAN, ESQ.
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